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Concurrent access to sucrose pellets decreases methamphetamine-seeking behavior in Lewis rats

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ABSTRACT

Investigation of the role of choice between use of drugs of abuse and pursuit of alternative non-drug reinforcers is receiving greater attention. An understanding of the determinants influencing choice between drugs and alternative reinforcers will eventually lead to an understanding to the neural substrates of the drug altered brain. We investigated the impact of concurrent access to sucrose pellets on methamphetamine self-administration and self-regulated reinstatement of methamphetamine seeking following extinction training in Lewis rats. Our results from the self-administration experiment show that rats with concurrent access to sucrose self-administered significantly less methamphetamine compared to the methamphetamine only group. For our extinction/reinstatement experiment, concurrent access to sucrose during self-regulated methamphetamine reinstatement reduced methamphetamine intake and non-reinforced methamphetamine-seeking behavior in rats compared to rats that received access to just methamphetamine. These findings indicate that concurrent access to alternative reinforcers during various stages of methamphetamine-seeking behavior robustly decreased methamphetamine intake and serves as a valid rodent choice paradigm.

1. Introduction

Persons addicted to psychostimulants readily choose drugs over other reinforcers: family, work, or avoiding incarceration (Kalivas and Volkow, 2005). Choice is rarely modeled in rodent extinction/reinstatement paradigms seeking to model craving and relapse in humans addicted to psychostimulants. Choice paradigms with rats could potentially provide better preclinical evaluation of the cognitive and behavioral mechanisms involved in the neural plasticity induced by psychostimulant self-administration and abuse. Choice paradigms might also show higher efficacy in predicting therapeutic drug effects on craving in humans because they actually measure mechanisms influencing response allocation between drugs and alternative reinforcers (e.g. Negus, 2003). Concurrent schedules of reinforcement/choice behavior between food and psychostimulants have been successfully demonstrated in non-human primates (e.g. Comer et al., 1994; Paronis et al. 2002; Negus 2003; Gasior et al., 2004) and rats (e.g. Kearns et al., 2007). However, the evaluation of choice in methamphetamine self-administration and reinstatement of methamphetamine-seeking behavior following extinction training in rats has not been extensively studied.

The goal of the present study was to establish choice procedures between methamphetamine-seeking behavior and responding for sucrose pellets in rats. The two facets of methamphetamine-seeking behavior we sought to measure were: 1) choice between methamphetamine and sucrose pellets during ongoing methamphetamine self-administration, and 2) self-regulated methamphetamine reinstatement following extinction training.

2. Methods

2.1. Subjects

Twenty-eight Lewis (LEW) rats (Harlan, Indianapolis, IN) weighing 250–300g upon arrival were used in this study. Rats were housed individually and maintained in a 12/12h light/dark cycle (lights on 0700h). Rats received unlimited access to tap water and were maintained at approximately 95% of their free-feeding weight throughout both experiments. All protocols were approved by the Medical College of Georgia's Institutional Animal Care and Use Committee, and complied with "Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research" (National Research Council, 2003).

2.2. Drugs

Methamphetamine HCl (methamphetamine; Sigma, St. Louis, MO) was dissolved in sterile physiological saline and filtered (0.2μm). The

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infusion bolus used for self-administration was 0.05ml/infusion. In order to determine catheter patency in animals demonstrating irregular self-administration or self-regulated methamphetamine reinstatement behavior, pentobarbital sodium (50mg/ml; Ovation Pharmaceuticals, Deerfield, IL) was intravenously infused in a bolus of 0.1ml (5-mg total dose). This concentration of iv pentobarbital induces loss of righting reflex that recovers after approximately 10min.

2.3. Apparatus

Experiments were conducted in 16 operant chambers (Coulbourn Instruments, Allentown, PA). Chambers were housed in sound-attenuated cubicles. The chambers contained two retractable levers, a pellet hopper, and a house light located outside the chamber. Intravenous (iv) methamphetamine was delivered through liquid swivels (Instech, Plymouth Meeting, PA) by infusion pumps (model A73-02-SEL, Razel Scientific Instruments, St. Albans, VT). The behavioral programs, pumps, and data collection were controlled by a computer (Colbalt, Allentown, PA) with Graphic State Notation 3.0 software (Coulbourn Instruments, Allentown, PA).

2.3.1. Lever training

Rats in both experiments were food restricted to approximately 95% of their free-feeding weights and trained to lever press for 45-mg sucrose pellets (Formula F0042, Bio-Serv, Frenchtown, NJ) during daily 1-h sessions. Lever presses on one lever were reinforced using a continuous reinforcement schedule and responding on an adjacent lever resulted in no programmed consequences. Successful lever training was defined as earning ≥ 100 sucrose pellets in a single session. We removed the metal food hoppers and replaced them with a metal plate following successful lever training for groups that did not have concurrent access to sucrose.

2.3.2. Surgery

Rats were implanted with silastic catheters according to previously described methods (Kruzich and Xi, 2006). Rats were anesthetized with 90-mg/kg ketamine and 1.6-mg/kg xylazine. Animals received 7days to recover from surgery. Catheters were flushed daily by administering 0.1ml of 100-U/ml heparinized saline.

2.4. Experiment #1: methamphetamine versus sucrose dose response curve

Following surgical recovery, rats were allowed to self-administer methamphetamine (0.06mg/kg/iv/infusion) during 2-h sessions 7days a week. One lever was assigned as the methamphetamine lever, and the adjacent lever was the "sucrose pellet" lever for the METH + Sucrose subjects for the remainder of the experiment. Locations of methamphetamine and sucrose pellet levers were counterbalanced across subjects in all groups. Reinforced responses for methamphetamine resulted in 5-s infusions (0.06mg/kg/iv in a volume of 0.05ml) plus 5s of additional timeout (10-s total timeout). Responding on the sucrose pellet reinforced lever was reinforced along a continuous schedule of reinforcement without a programmed timeout. However, a change-over-delay (COD) was used between levers when a methamphetamine injection was earned; receipt of reinforcement on one lever precluded access to sucrose during the 10-s timeout. This strategy was taken in order to prevent simultaneous reinforcement and to decrease the frequency of "switching" in order to receive the alternative reinforcer. Responses emitted during the infusions, stimulus presentations, timeouts, or COD resulted in no programmed consequences, but were recorded.

2.4.1. Experiment 1: dose response curve

After demonstrating stable intake along the concurrent schedules of reinforcement, defined as minimum of 7days of self-administration where sucrose and methamphetamine intake did not vary by 20%, rats were given access to different doses of METH for a minimum of 5days/dose. The doses used were 0.01, 0.03, 0.06, and 0.1mg/kg/iv/infusion. The dosing order was randomized across all subjects. After completing one dose, the rats were returned to the training concentration (0.06mg/kg/iv) until responding returned to baseline values determined by the individual subject prior to measuring dose-dependent behavior. The amount of sucrose pellet reinforcement available during self-administration and generation of the dose–response curve did not vary.

2.5. Experiment 2: choice between food and self-regulated methamphetamine reinstatement

2.5.1. Methamphetamine self-administration

Rats were lever trained with sucrose pellets prior to initiating the methamphetamine self-administration phase of the experiment. Rats self-administered methamphetamine (0.06mg/kg/iv/infusion) for a minimum of 14days. Responding could not vary by over 20% during self-administration, a minimum of 10 infusions per session had to be earned, and 85% of responding had to occur on the "active lever" during self-administration.

2.5.2. Extinction

Following methamphetamine self-administration testing, rats underwent extinction sessions. During daily 2-h extinction sessions, responding on either lever resulted in no programmed consequences. The syringe pump was disengaged during extinction sessions. The syringe pump mostly likely did not serve as a cue to the subjects because infusion noise did not register inside the chambers during sound testing with a sound meter (Extech, Waltham, MA; data not shown). Therefore, the only discriminative cues missing during extinction relative to self-administration were the interoceptive cues associated with methamphetamine administration and intravenous injections. All responses emitted by the METH Only group during extinction session were recorded. Rats in the METH + Sucrose group received access to 45-mg sucrose pellets on the formerly inactive lever (the lever opposite of the methamphetamine reinforced lever). Responding on the METH lever resulted in no programmed consequences during extinction sessions for the METH + Sucrose group of rats. All rats underwent a minimum of 5days of extinction training prior to starting self-regulated methamphetamine reinstatement. Obtainment of extinction training was further operationally defined as emitting 10 or fewer responses on the previously methamphetamine reinforced lever during a single 2-h extinction session.

2.5.3. Self-Regulated methamphetamine reinstatement

We provided rats with limited access to fixed doses of methamphetamine during self-regulated methamphetamine reinstatement. The available doses for methamphetamine reinstatement were: 0.0 (saline access), 0.12mg/kg/iv total dose, 0.24mg/kg/iv total dose, 0.6mg/kg/iv and 1.2mg/kg/iv total dose access. Responding was reinforced along an FR-1 schedule of reinforcement followed by a 10-s timeout (5-s for infusion + an additional 5-s timeout). The methamphetamine concentration of each individual infusion was 0.06mg/kg. Therefore, a 0.12mg/kg/iv dose test session meant that the first 2 responses that met the schedule requirements resulted in a methamphetamine infusion. For 0.6mg/kg, 10 infusions were available under an FR-1 10-s timeout schedule of reinforcement, etc. The reinforced responses could take place at any time during the session, based on the individual subject's own "choice". Once all of the possible infusions were earned by the individual rat, all subsequent responses on the methamphetamine lever went unreinforced for the remainder of the test session and resulted in no programmed consequences, but the subject could continue to respond for sucrose pellets. Each rat was tested at each dose once. Dosing order was randomized by use of a Latin Squares procedure.

2.6. Statistics

Methamphetamine infusions (group × session), number of responses emitted during access to various doses of methamphetamine (group ×

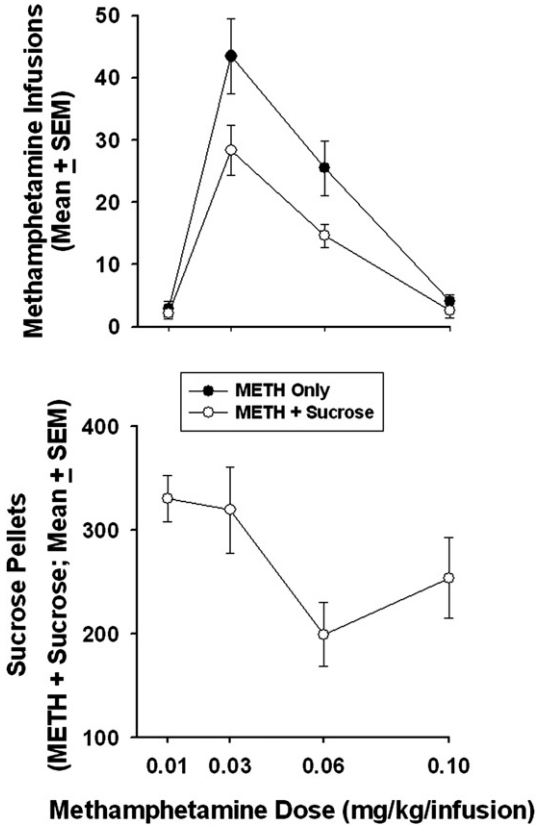

Fig. 1. Methamphetamine dose–response curve. *Top*: concurrent access to sucrose pellets significantly reduced methamphetamine intake ($F=5.0$; $p<0.05$). There was a significant effect of "Dose" on intake ($F=55.0$; $p<0.001$) yet the "Group×Dose" interaction was insignificant ($F=2.8$; $p>0.05$). Please see text for full description of significant group differences. *Bottom*: Sucrose pellets earned by the "METH+Sucrose" group during METH self-administration across the various doses. The influence of methamphetamine dose did not statistically alter the number of pellets earned ($p=0.1$).

dose), responding during methamphetamine-reinstatement tests (group × dose) were analyzed with separate repeated measures (RM) analyses of variance (ANOVA) tests. If a significant RM-ANOVA was determined, post-hoc comparisons utilizing the Tukey Test were performed. Significance was set at $p < 0.05$. In order to determine quantitatively if the rate of extinction differed between groups, a Log-Rank Kaplan–Meier Survival Analysis was used. The simple criterion for exclusion for this analysis was "number of days to 10 or fewer responses" for an extinction session.

3. Results

3.1. Experiment #1: methamphetamine self-administration versus sucrose pellets

3.1.1. Experiment #1: methamphetamine intake during baseline conditions

The groups did not differ in body weight throughout this experiment. We analyzed methamphetamine intake between the group that had sole access to methamphetamine (METH Only) and the second group that had concurrent access to methamphetamine and 45mg sucrose pellets (METH + Sucrose) for the 5-sessions prior to generating the dose response curve (intake was the most stable for both groups during this timeframe; data not shown). There was a significant effect of "group" on intake ($F(1,12) = 4.4$; $p = 0.05$), with the METH Only consuming the most methamphetamine ($p < 0.05$). Intake was not influenced by session ($F = 1.1$). There was no significant interaction between session × group for intake ($F = 0.5$).

3.1.2. Methamphetamine versus sucrose pellets dose response curve

There was a significant effect of "group" on dose-dependent intake (Fig. 1; $F(1,12) = 4.9$; $p < 0.05$). The METH Only group self-administered more METH than the METH + Sucrose group ($p < 0.05$). There was a significant effect of "dose" on intake ($F(3,36) = 55.3$; $p < 0.001$). The rats self-administered less infusions when given access to 0.01mg/kg/iv/infusion compared to all of the other doses tested ($p < 0.05$ for all comparisons). The highest number of infusions occurred when rats had access to 0.03mg/kg/iv compared to all of the doses tested ($p < 0.05$ for all comparisons). Rats self-administered significantly more infusions when give access to 0.06mg/kg/infusion METH compared to 0.01 or 0.12mg/kg/infusion METH. There was a significant trend for a group × dose interaction ($F(3,36) = 2.8$; $p = 0.055$). The METH Only group self-administered significantly more infusions when give access to 0.03 and 0.06mg/kg/infusion compared to the METH + Sucrose group ($p < 0.05$ for all comparisons).

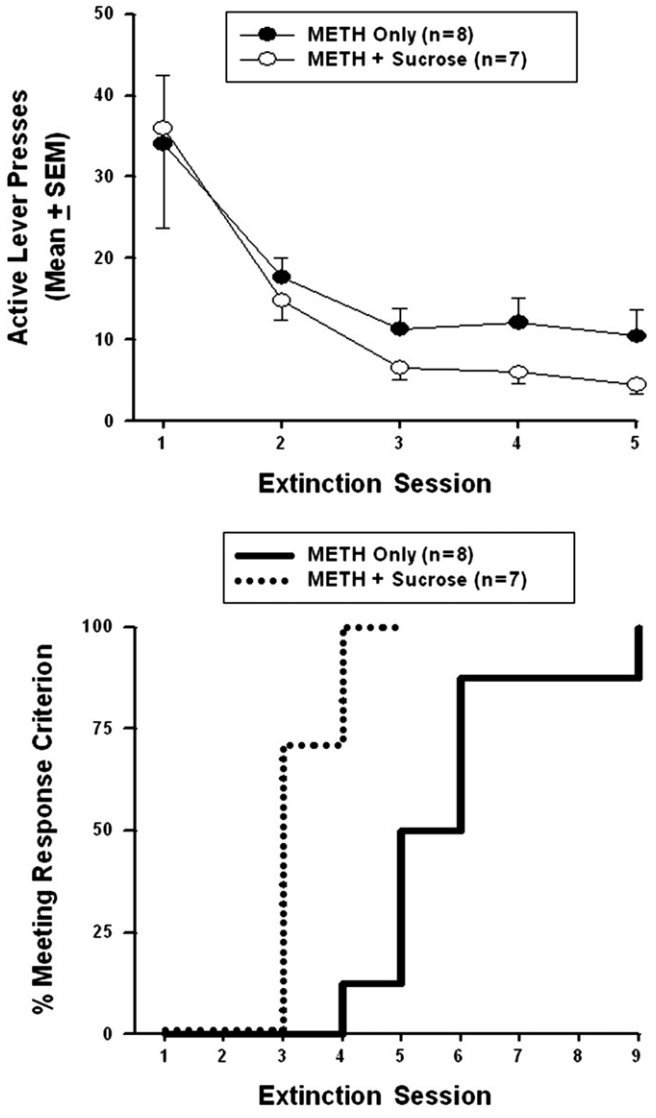

Fig. 2. Extinction responding and survival analysis. *Top*: the METH Only and METH+Sucrose groups did not significantly differ in response output during the first 5 days of extinction sessions. Both groups did demonstrate a significant reduction in response output during sessions 4 and 5 compared to sessions 1 and 2 ($p<0.05$ for all comparisons). *Bottom*: the rats in the METH+Sucrose group met our response criterion for extinction learning (10 or fewer responses per 2-h session) significantly faster than the METH Only group ($*p<0.001$).

3.2. Experiment #2: self-regulated methamphetamine reinstatement

3.2.1. Extinction: overall comparison

The groups did not differ in response output during extinction (Fig. 2, Top; $F(1,13) = 0.7$; $p > 0.4$). Expectedly, there was an effect of "session" on extinction training response output ($F(4,52) = 11.9$; $p < 0.01$). Response output during sessions 4 and 5 were significantly lower than during sessions 1–3 ($p < 0.05$ for all comparisons). There was not a significant group × session interaction ($F(4,52) = 0.3$; $p > 0.9$). All of the subjects from the METH + Sucrose group terminated extinction training after session #5 because they attained the extinction criteria: minimum of 5 sessions and no more than 10 responses per 2-h extinction session. A number of the METH Only rats required more extinction sessions (please see below and Fig. 2 for thorough explanation).

3.2.2. Extinction: survival analysis

During the course of the experiment, we noticed that the METH + Sucrose rats were obtaining our extinction criteria for responding (10 or fewer responses/session) faster than the METH Only group (Fig. 2, bottom). In order to examine this statistically and quantitatively, we used the Kaplan–Meier Survival Analysis. This analysis revealed that the METH + Sucrose group did indeed reach our response criteria faster than the METH Only group if we ignore the "minimum of 5days" criterion ($X^2(1) = 13.7$; $p < 0.001$).

3.2.3. Self-regulated METH reinstatement

There was a significant effect of "group" on response output during self-regulated METH reinstatement ($F(1,13) = 13.04$; $p < 0.01$) (Fig. 3). The METH + Sucrose group emitted significantly fewer responses for methamphetamine than the METH Only group ($p < 0.05$). There was a significant effect of "total available dose" on responding ($F(4,52) = 12.42$; $p < 0.001$). Rats did not differ in response output when given access to saline or 0.12mg/kg methamphetamine ($p > 0.4$). However, access to saline and 0.12mg/kg methamphetamine resulted in the lowest behavioral output compared to all the other doses tested ($p < 0.05$ for all comparisons). Response levels during access to 0.24, 0.6, or 1.2mg/kg did not statistically differ ($p > 0.05$ for all comparisons). There was a significant group × dose interaction ($F(4,52) = 5.54$; $p < 0.001$). For the within group comparisons, 0.24, 0.6 and 1.2mg/kg/total dose elicited significantly greater response output compared to saline and 0.12mg/kg methamphetamine in the METH Only group ($p < 0.05$ for all comparisons). Access to 0.6mg/kg methamphetamine resulted in more responses compared to access to 0.24mg/kg in the METH Only group ($p < 0.05$ for all comparisons). Response output did not differ for the METH Only rats when given access to 0.6 or 1.2mg/kg ($p > 0.15$).

For the between groups comparisons for self-regulated reinstatement, robust differences were found. The METH Only rats emitted more responses than the METH + Sucrose rats following 0.24, 0.6, and 1.2mg/kg METH access ($p < 0.05$ for all comparisons). The groups did not differ in response output when both had access to saline or 0.12mg/kg methamphetamine ($p > 0.05$ for all comparisons).

3.2.4. Sucrose pellet intake during self-regulated METH reinstatement

There was a significant effect of METH dose on sucrose pellet intake during self-regulated METH reinstatement for the METH + Sucrose group ($F(4,24) = 9.25$; $p < 0.001$). There was a significant decrease in sucrose pellets earned during the 0.12 and 0.24mg/kg access tests compared to all other doses tested ($p < 0.05$ for all comparisons). Food lever response output did not differ when given access to 0.12 or 0.24mg/kg during self-regulated METH reinstatement ($p > 0.9$).

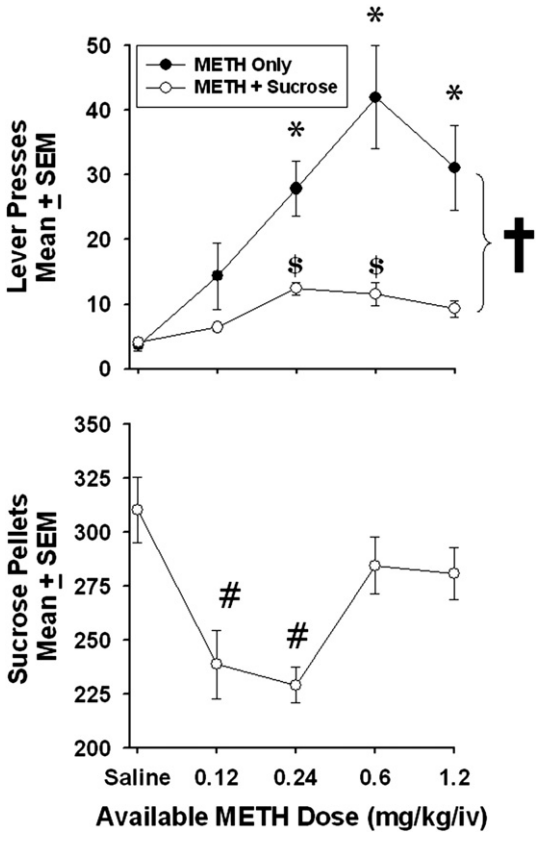

Fig. 3. Self-regulated METH Reinstatement. *Top*: dose-dependent behavioral output during access to various fixed doses of methamphetamine following extinction sessions. Concurrent access to sucrose pellets significantly reduced methamphetamine-seeking behavior ($^{\dagger}p<0.05$). Response output was influenced by the available dose ($F=12.4$; $p<0.001$); access to 0.12, 0.6, and 1.2 mg/kg/iv significantly reinstated responding in the METH Only group ($^{*}p<0.05$) whereas just 0.24 and 0.6 mg/kg/iv methamphetamine increased responding for drug in the METH+Sucrose Group ($^{\$}p<0.05$). There was a significant Group×Dose interaction ($F=5.5$; $p<0.001$). *Bottom*: The number of sucrose pellets earned during self-regulated methamphetamine reinstatement was influenced by the available methamphetamine dose; to 0.12 and 0.24 mg/kg/iv methamphetamine significantly reduced responding for sucrose pellets compared to all other doses tested ($^{\#}p<0.05$ for all comparisons).

4. Discussion

The present study highlights the effects of receiving concurrent access to sucrose during active methamphetamine self-administration and during the clinically relevant self-regulated reinstatement procedure. Concurrent access to sucrose during both paradigms was very effective in curbing methamphetamine-seeking behavior; methamphetamine intake during concurrent access to sucrose pellets was at levels typically associated with administering drugs that block the central effects of psychostimulants on the brain (e.g. Caine and Koob, 1994; See et al., 2001).

The ultimate objective of this study was to determine the patterns of choice between a fixed alternative reinforcer and varying concentrations of available methamphetamine during active self-administration and in an extinction/reinstatement paradigm. While earlier studies have elegantly documented choice between psychostimulants and food in non-human primates (e.g. Aigner and Balster, 1978; Neguss, 2003) little is know regarding behavioral patterns of specifically methamphetamine intake when an alternative reinforcer is concurrently available in rats. We acknowledge that numerous permutations could be performed regarding varying the degree of food access and methamphetamine access—however, a detailed survey of that magnitude is beyond the scope of the present study. In previous choice paradigms (e.g. Negus, 2003) a set number of reinforcers were available prior to terminating a session and determining the percent choice of food versus drugs of abuse. In our

paradigm, subjects could respond for as many reinforcers as session length permitted. The procedural differences between Negus (2003) and the present study most likely influenced the disparities in results. The increased sucrose pellet consumption seen at the higher doses of methamphetamine available could indeed indicate that methamphetamine was having a direct effect on sucrose pellet responding and consumption in our paradigm (see Katz and Higgins, 2003, for full explanation of direct effects).

Current pharmacological reinstatement paradigms utilizing rats are straightforward and attempt to model drug craving and subsequently relapse; rats self-administer drugs of abuse such as methamphetamine for a number of days, rats then undergo extinction training. During one of the extinction sessions, the experimenter picks up the rat, injects the rat in the peritoneum with methamphetamine, and then places the rat in a self-administration chamber. The number of responses emitted by the rat following the passive injection serves as an index of relapse (e.g. Davis and Smith 1976). However, when previously abstinent humans addicted to psychostimulants experience pharmacological relapse, it is triggered by active self-administration and not unexpected passive priming (Dackis and O'Brien 2001). The reliance on passive priming in preclinical models of craving and relapse may actually lead to preclinical false positives that will negatively impact subsequent clinical trials (O'Brien, 2005). Recent studies with rats demonstrated a remarkable ability of *N*-acetylcystein to disrupt passively primed reinstatement of cocaine-seeking behavior (e.g. Baker et al. 2003). However, *N*-acetylcystein only marginally reduced cocaine craving in human cocaine addicts at high doses (LaRowe et al., 2007; Mardikian et al. 2007). Potentially, future false positives could be avoided with utilization of choice paradigms.

A prior study with male cynomolgus monkeys formerly trained to self-administer cocaine and then trained to respond for either saline or food in a concurrent availability paradigm reported that passive injections of cocaine significantly shifted responding away from food towards responding on the previously cocaine reinforced lever (Banks et al., 2007). In the present study, access to higher total doses of methamphetamine actually led to more sucrose pellet consumption. One factor that may have contributed to the differences in results could be the actual control of administration; in the Banks et al. study (2007), subjects were passively primed whereas subjects had active control over intake in the present study. Therefore, established differences in neuronal signaling demonstrated between passive administration and active self-administration/drug-seeking behavior (Hemby et al., 1997; Lecca et al., 2007) should be considered when trying to rectify the contradictory results between Banks et al. (2007) and the present study.

The ability of extinction training to alter neural circuitry and to decrease drug-seeking behavior in preclinical models of craving and relapse is receiving burgeoning interest (e.g. Self et al., 2004). The presence of an alternative reinforcer, sucrose pellets, and extinction training may have diminished or devaluated the drive to maintain methamphetamine-seeking behavior during extinction training and reinstatement testing in experiment 2. In most devaluation tasks, animals are either pretreated with one of two reinforcers prior to a testing session, which typically decreases responding for the preloaded reinforcer and increases responding for the alternative reinforcer (e.g. Johnson et al., 2007). An additional method of reinforcer devaluation is to pair an aversive stimulus or unexpected outcome with expected reinforcer delivery (e.g. Kerfoot et al., 2007). Possibly, the new learning associated with extinction training and access to an alternative reinforcer in the present study shifted behavior away from the formerly methamphetamine paired lever to the sucrose reinforced lever—our procedure at the very least could be considered a devaluation procedure. While this approach is an initial step at increasing the predictive and construct validity of preclinical craving and relapse models, future studies should include parametric evaluations of different doses of methamphetamine versus food and response requirements for either reinforcer in order to increase the validity of this paradigm (Katz and Higgins, 2003).

In conclusion, rats quickly learned our concurrent schedules of reinforcement procedure. Behavioral output demonstrated by rats during self-regulated methamphetamine reinstatement in the "METH Only" group was robust and replicated our earlier findings with mice (Kruzich, 2007). Based on the results from the present study and our past research (Kruzich, 2007), we argue that use of self-regulated reinstatement and choice should be incorporated to understand the mechanisms underlying craving and relapse to drug-seeking behavior.

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