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Persistent palatable food preference in rats with a history of limited and extended access to methamphetamine self-administration

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Abstract

Recent studies have shown that when given a mutually exclusive choice between cocaine and palatable foods most rats prefer the non-drug rewards over cocaine. Here, we used a discrete choice procedure to assess whether palatable food preference generalizes to rats with a history of limited (3 hr/day) or extended (6 or 9 hr/day) access to methamphetamine self-administration. On different daily sessions, we trained rats to lever-press for either methamphetamine (0.1–0.2 mg/kg/infusion) or palatable food (5 pellets per reward delivery) for several weeks; regular food was freely available. We then assessed food-methamphetamine preference either during training, after priming methamphetamine injections (0.5–1.0 mg/kg), following a satiety manipulation (palatable food exposure in the home cage), or after 21 days of withdrawal from methamphetamine. We also assessed progressive ratio responding for palatable food and methamphetamine. We found that independent of the daily drug access conditions and the withdrawal period, the rats strongly preferred the palatable food over methamphetamine, even when they were given free access to the palatable food in the home cage. Intake of methamphetamine and progressive ratio responding for the drug, both of which increased or escalated over time, did not predict preference in the discrete choice test. Results demonstrate that most rats strongly prefer palatable food pellets over intravenous methamphetamine, confirming previous studies using discrete choice procedures with intravenous cocaine. Results also demonstrate that escalation of drug self-administration, a popular model of compulsive drug use, is not associated with a cardinal feature of human addiction of reduced behavioral responding for non-drug rewards.

Keywords

psychostimulants; palatable food; discrete choice; preference; self-administration; extended access; limited access; progressive ratio; drug priming; food satiety

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Introduction

In humans, cocaine and methamphetamine addiction is characterized by a progressive increase or escalation of psychostimulant use, increased motivation to seek the drugs, compulsive drug seeking despite negative consequences, and reduced behavioral responding for non-drug rewards or diminished control over behavior by non-drug rewards (American Psychiatric Association, 2013; Goldstein and Volkow, 2002; Kalivas et al., 2005).

In preclinical studies, extended access drug self-administration procedures (typically > 6 hr/day) are used to model these clinical features of psychostimulant addiction (Ahmed and Koob, 1998; Bozarth and Wise, 1985; Johanson et al., 1976; Morgan et al., 2002; Tornatzky and Miczek, 2000; Yokel and Pickens, 1973). Results from many studies have shown that rats trained under extended but not limited (typically 1–2 hr/day) access conditions show escalation of cocaine and methamphetamine intake (Ahmed and Koob, 1998; Kitamura et al., 2006), increased motivation to seek the drugs, as assessed by the progressive ratio reinforcement schedule (Lenoir and Ahmed, 2008; Wee et al., 2007), and drug self-administration despite adverse consequences, as assessed in a resistance to punishment or related procedures (Ahmed, 2012; Vanderschuren and Everitt, 2004). These observations support the notion that extended access drug self-administration procedures model human psychostimulant addiction (George et al., 2014).

However, from the perspective of modelling addiction, drug self-administration procedures, in which the only reward available in the operant chambers is an intravenous drug injection, deviate significantly from the human condition where compulsive drug use often occurs in the presence of alternative non-drug rewards and drug-seeking behavior is chosen over behaviors aimed at pursuing those non-drug rewards (Ahmed et al., 2013b; Hyman and Malenka, 2001). Based on this premise, and limitations related to the use of rate-dependent measures to assess the rewarding efficacy of drugs (Banks and Negus, 2012; Hursh, 1980), over the years behavioral pharmacologists have developed rate-independent choice (food versus drug) procedures to assess the reinforcing efficacy of abused drugs (Carroll, 1993; Nader and Woolverton, 1991; Woolverton and Balster, 1979), see also (Spragg, 1940) for an early use of a choice procedure.

Recently, Ahmed, Lenoir and colleagues have used a discrete choice procedure in which one lever is paired with an intravenous infusion of cocaine and another lever is paired with a sweet saccharin solution (Ahmed et al., 2013b). A surprising finding from these studies was that over 90% of male rats with a history of either limited or extended daily access to cocaine (6 hr/day) over many weeks strongly preferred the saccharin solution over cocaine (Cantin et al., 2010; Lenoir et al., 2013; Lenoir et al., 2007). These data were extended to the choice of saccharin versus cocaine cues (Madsen and Ahmed, 2014) and were independently replicated by other investigators (Kerstetter et al., 2012; Perry et al., 2013; Tunstall and Kearns, 2013). A major finding in these studies was that neither escalation of drug intake nor responding on the progressive ratio schedule was associated with the preference measure (Ahmed et al., 2013a).

An important question that derives from the above findings is whether the persistent food preference generalize to other psychostimulant drugs like methamphetamine, a drug that is readily self-administered by laboratory rats (Yokel and Pickens, 1973). Previous studies have shown that concurrent access to food and methamphetamine decreases drug self-administration (Ettenberg, 2009), but whether or not palatable food is preferred over methamphetamine in a discrete choice procedure is unknown.

In the present study we used a discrete choice procedure (Lenoir et al., 2007) to determine palatable food versus methamphetamine preference in rats with a history of limited or extended access to methamphetamine. We also determined whether methamphetamine priming injections, a prolonged withdrawal period, or the availability of the palatable food in the home cage will decrease the strong food preference (see Results). Finally, we determined whether amount of drug intake or progressive ratio responding (Hodos, 1961; Richardson and Roberts, 1996) correlate with the preference measure.

Material and Methods

Subjects

We used male Sprague-Dawley rats (Charles River, Raleigh, n=45), weighing 300–350g prior to surgery. We grouped-housed (two per cage) the rats for 1–3 weeks prior to surgery and then individually-housed them after intravenous surgery. In Exp. 1–2, we housed the rats in the animal facility and brought them to their self-administration chambers for their daily sessions. In Exp. 3–4, we brought the rats to the self-administration chambers on the first training day and kept them in these chambers for the duration of the experiments. We maintained rats on a reverse 12 hr light/dark cycle (lights off at 8 AM) with free access to standard laboratory chow and water throughout the entire experiment. Our procedures followed the guidelines outlined in the Guide for the Care and Use of Laboratory Animals (eighth edition; http://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf). We excluded two rats due to catheter problems and one rat due to failure to acquire methamphetamine self-administration.

Intravenous surgery

We anesthetized rats with ketamine and xylazine (50 and 5 mg/kg, i.p., respectively) and inserted silastic catheters into the jugular vein as described previously (Bossert et al., 2009; Theberge et al., 2013). We attached the catheters to a modified 22-gauge cannula that was mounted to the rats' skulls using dental cement and stainless steel screws. We injected buprenorphine (0.1 mg/kg, s.c.) after surgery to relieve pain and allowed rats to recover for 7 days before methamphetamine or palatable food self-administration training. We flushed the catheters daily with 0.2 ml of sterile saline solution containing 1.0 mg of gentamicin (Butler Schein; 5 mg/mL).

Apparatus

We trained rats in self-administration chambers located inside sound-attenuating cubicles, fitted with an electric fan, and controlled by a Med Associates system. We equipped each chamber with a stainless steel grid floor and 2 operant panels placed on the left and right

walls. We equipped the left panel of the chamber with a discriminative stimulus (red light) that signaled the insertion and subsequent availability of the methamphetamine-paired active (retractable) lever. Presses on this lever activated the infusion pump and a discrete white cue light located above the lever for 20 sec. We delivered methamphetamine through a modified cannula (Plastics One) connected to a liquid swivel (Instech) via polyethylene-50 tubing that was protected by a metal spring. We equipped the right panel of the chamber with a discriminative stimulus (white house light) that signaled the insertion and subsequent availability of the food-paired active (retractable) lever. Presses on this lever activated the pellet dispenser and a discrete tone cue located above the lever for 20 sec; the 45 mg palatable food pellets were delivered to a pellet dispenser located near the food-paired lever. We equipped the right wall with an inactive (stationary) lever that had no reinforced consequences. We placed a bottle of water and a food hopper on the external and internal side of the chamber's transparent polycarbonate door, respectively (Figure 1).

Procedures

Methamphetamine self-administration—We trained rats to self-administer (+)-methamphetamine HCl (NIDA) during three-, six- or nine-1 hr daily sessions (see specific experiments below) that were separated by a 10 min off period, under a fixed-ratio-1 (FR1) 20-sec timeout reinforcement schedule; drug infusions were paired with the 20 sec discrete white light cue. This training procedure is based on previous studies (Krasnova et al., 2014; Shepard et al., 2004; Shepard et al., 2006). We started the self-administration sessions at the onset of the dark cycle and sessions began with the presentation of the red light and 10 sec later by the insertion of the methamphetamine-paired active lever; the red light remained on for the duration of the session and served as a discriminative stimulus for methamphetamine availability. At the end of each 1-hr session, the red light was turned off, and the active lever was retracted. In Exp. 3 (9 hr/day extended access), we gave the rats a day off after 3 consecutive methamphetamine self-administration sessions to prevent weight loss during the experiment (Krasnova et al., 2014; Theberge et al., 2013). We dissolved methamphetamine HCl in sterile saline and the rats self-administered the drug at a dose of 0.1 mg/kg/infusion over 3.5 sec (0.10 ml/infusion) (Shepard et al., 2004; Theberge et al., 2013). To prevent overdose, we limited the number of infusions to 15 per 1 hr.

Food pellets self-administration—Our palatable food training procedure was similar to that used for methamphetamine with the following exceptions. First, the lever presses under the FR1 20 sec timeout reinforcement schedule led to the delivery of five 45-mg 'preferred' or palatable food pellets (TestDiet, Catalogue # 1811155, 12.7% fat, 66.7% carbohydrate, and 20.6% protein); pellet deliveries were paired with the 20-sec discrete tone cue. Second, prior to the first 1–2 formal operant training sessions, we gave the rats 1-hr magazine training sessions during which 5 pellets were delivered non-contingently every 5 min. We started the self-administration sessions at the onset of the dark cycle and sessions began with the presentation of the white house light and 10 sec later by the insertion of the food-paired active lever; the white house light remained on for the duration of the session and served as a discriminative stimulus for the palatable food. At the end of the session, the white light was turned off and the active lever was retracted.

Investigators have been using the 'preferred' TestDiet pellet type in recent food reinstatement studies (Calu et al., 2013; Cifani et al., 2012; Pickens et al., 2012), because in food preference tests, rats prefer this type of pellet over other pellet types with different compositions of fat and carbohydrate, and different flavors (Calu et al., 2014). Based on a previous study (Krasnova et al., 2014), we chose 5 pellets per reward delivery in order to roughly equate the number of food and methamphetamine rewards earned per day and consequently the number of CSs (tone or light-cue)—UCSs (methamphetamine, food) pairings during training.

Progressive ratio test—We conducted all progressive ratio tests using the same parameters (e.g., dose of methamphetamine, number of palatable food pellets per reward, stimuli associated with the two retractable levers) that we used during the self-administration training phase. During the progressive ratio sessions, we increased the ratio of responses per rewards or infusions (food pellets or methamphetamine respectively) according to the following sequence: 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, etc.) (Richardson and Roberts, 1996). The final completed response ratio represents the "breaking point" value.

Discrete-trials choice procedure—We conducted the discrete choice sessions using the same parameters (dose of methamphetamine, number of palatable food pellets per reward, stimuli associated with the two retractable levers) that we used during the training phase. We allowed rats to choose between the methamphetamine- and a palatable food-paired lever in a discrete-trials choice procedure similar to the one used by Lenoir and Ahmed (Lenoir and Ahmed, 2008; Lenoir et al., 2007). We divided each 180 (Exp. 1–2) or 200 (Exp. 3–4) min choice sessions into 18 or 20 discrete trials that were separated by 10 min. We chose this interval because it is longer than the inter-infusion interval under our training conditions (about 5–7 min) and thus preventing a potential confound of drug 'satiety', which can bias choice toward the food. Drug 'satiety' periods between consecutive drug injections (analogous to food satiety periods between consecutive food deliveries) are largely controlled by fluctuations in brain drug levels and are highly correlated with dopamine levels in nucleus accumbens (Tsibulsky and Norman, 1999; Wise et al., 1995). According to Tsibulsky and Norman (2011), the inter-infusion interval during psychostimulant self-administration is determined by within-session drug craving that is maximal when drug accumulated from previous injections is metabolized below a "satiety threshold." We also chose the 10 min inter-choice interval over shorter time periods in order to reduce the direct anorexigenic effect of methamphetamine accumulation on food intake (Bittner et al., 1981) and consequently food choice.

Each trial began with the presentation of both discriminative stimuli previously associated with palatable food or methamphetamine followed 10 sec later by the insertion of both palatable food- and methamphetamine-paired levers. Rats then had to select one of two levers. If rats responded within 8 min, they received the reward corresponding with the selected lever. Reward delivery was signaled by the methamphetamine or food CS (white cue light or tone, respectively), the retraction of both levers, and the turning off of both food- and methamphetamine discriminative stimuli. If a rat failed to respond on either active

lever within 8 min, both levers were retracted and their related discriminative stimuli were extinguished with no reward delivery. [Note: we did not counterbalance the discrete cues for food and methamphetamine, because in both pilot and previous studies in the lab we found that training rats for drug self-administration takes significantly more time without the discrete white cue light above the drug-paired lever while the type or availability of a discrete cue has little impact on food self-administration training following magazine training. Consequently, we did not counterbalance the discriminative cues to avoid having a white house light together with a discrete white cue light in the same session. Also, in pilot studies without any discrete cue light we found strong preference for the food pellets and we were hoping to decrease this preference by making the intravenous methamphetamine delivery a more salient event to the rat.]

Specific experiments

Exp. 1: Food versus methamphetamine preference after limited access (3 hr/day) to food and methamphetamine self-administration (Fig. 2A)—The experiment consisted of three phases: Training phase, progressive ratio tests, and discrete choice tests under different conditions.

Training: We trained rats (n=13) to self-administer palatable food pellets (5 pellets/reward delivery) and methamphetamine (0.1 mg/kg/infusion) for 3 hr/day on alternate days, over 14 days.

Progressive ratio: We determined progressive ratio responding for food and methamphetamine in 3 hr sessions over 6 consecutive days (3 sessions for food and 3 sessions for methamphetamine on alternate days).

Discrete choice tests: We first determined food versus methamphetamine choice over 3 consecutive days immediately after the progressive ratio tests and after 21 days during which we kept the rats in the animal facility and handled them twice a week. Next, we tested food versus methamphetamine choice on 3 consecutive days after priming injections of saline and methamphetamine (0.5 and 1.0 mg/kg, i.p.; 15 min pretreatment time) using an ascending order dose-response curve. We chose the methamphetamine priming dose based on previous studies using the reinstatement procedure (Gass et al., 2009; Schwendt et al., 2009). Finally, on the last 3 choice tests we provided the rats with access to the palatable food pellets for 1, 3 and 24 hr/day in their home cage, a satiety or devaluation manipulation (Dickinson et al., 1996), immediately before the choice tests. We gave the rats 50 g of the pellets in a ceramic bowl in their home cage.

Exp. 2: Food versus methamphetamine preference during limited (3 hr) and extended (6 hr) access to food and methamphetamine self-administration (Fig. 3A)—In Exp. 1 we observed strong preference for the food in rats trained to self-administer the food and methamphetamine rewards under limited (3 hr/day) access conditions. In Exp. 2, we determined whether we can increase methamphetamine preference by increasing the session duration to 6 hr/day and by increasing the unit dose of methamphetamine from 0.1 to 0.2 mg/kg/infusion.

The experiment consisted of two phases: Training and choice tests under limited access conditions (3 hr/day, 0.1 mg/kg/infusion, n=8) and subsequent training and choice tests under extended access conditions (6 hr/day, 0.1 and 0.2 mg/kg/infusion). During both phases, we train the rats to self-administer the food or methamphetamine on alternate days and tested them in the discrete choice procedure once a week. We first trained the rats under the limited access conditions for 12 days and then under the extended access conditions for 18 days (12 days with the 0.1 mg/kg unit dose and 6 days with the 0.2 mg/kg unit dose).

Exp. 3: Food versus methamphetamine preference during extended access (9 hr/day) to methamphetamine and food self-administration (Fig. 4A and 5A)—In Exp. 1–2 we observed strong preference for the palatable food in rats trained to self-administer the food and methamphetamine under both limited (3 hr/day) and extended (6 hr/day) access conditions on alternate days. In Exp. 3, we determined whether we can increase the preferences for methamphetamine by increasing the session duration to 9 hr/day, which induces strong escalation of drug intake (Krasnova et al., 2014; Theberge et al., 2013), and by training the rats to self-administer methamphetamine (and food) on consecutive rather than alternate days.

In Exp. 3a, we first trained rats (n=16) to self-administer food pellets for 6 days and then trained them to self-administer methamphetamine for 15 days. During methamphetamine self-administration training, we determined food versus methamphetamine choice every 3 days (5 tests) and also determined progressive ratio responding during 3 test sessions (Fig 4A). In Exp. 3b, we first trained rats (n=5) to self-administer methamphetamine for 15 days and then trained them to self-administer food pellets for 15 days. During food self-administration training, we determined food versus methamphetamine choice every 3 days (5 tests) and also determined progressive ratio responding during 3 test sessions (Fig 5A).

Statistical analyses

We analyzed the data with the statistical program SPSS and followed significant effects ($p<0.05$) with SPSS post-hoc contrasts within the repeated measures ANOVA module. For both the training phase and progressive ratio tests, the repeated-measures mixed ANOVA for rewards earned included the within-subjects factors Reward type (food, methamphetamine) and Session. For the choice tests, we normalized at 0 the indifference level between palatable food pellets and methamphetamine (preference score) using the following formula: 1 - (% drug choices/50%) (Lenoir et al., 2007) and analyzed the data with repeated-measures ANOVA using the within-subjects factor Choice session.

Results

Exp. 1: Food versus methamphetamine preference after limited access (3 hr/day) to food and methamphetamine self-administration (Fig. 2)

Food and methamphetamine training: The rats increased their reward intake over days, an effect that was more pronounced for the food reward (Fig. 2B). The repeated measures ANOVA, using the factors of Session and Reward type, showed a significant interaction between the two factors [$F(6,72)=5.9$; $p<0.01$)].

Progressive ratio tests: Progressive ratio responding increased over days for both food and methamphetamine, an effect that was more pronounced for the food reward (Fig. 2C). The repeated measures ANOVA showed a significant interaction between Session and Reward type [$F(2,24)=4.9$; $p<0.05$].

Discrete choice tests: The rats demonstrated a strong preference for food, which increased over time during the initial 3 tests (Fig. 2D). The statistical analysis of the preference score showed a significant effect of Choice session [$F(2,24)=7.6$; $p<0.05$]. After 21 withdrawal days, the rats continued to demonstrate strong food preference ($p<0.01$, Fig. 2D). Additionally, the food preference was not affected by methamphetamine priming injections prior to the choice test sessions ($p>0.1$, Fig. 2D). Finally, in the satiation (or devaluation) test, we found that exposing rats to the palatable food pellets for 1, 3, or 24 hr decreased food preference in an exposure-dependent manner (main effect of Exposure duration [$F(3, 33)=4.4$; $p<0.05$]. However, even after 24 hr of free access to the pellets in the home cage, the rats still preferred food over methamphetamine ($p<0.01$, Fig. 2D).

Exp. 2: Food versus methamphetamine preference during limited (3 hr) and extended (6 hr) access to food and methamphetamine self-administration (Fig. 3)

Food and methamphetamine training: The number of food rewards earned remained relatively stable during the 30 alternating (food, methamphetamine) training sessions. The number of methamphetamine rewards earned was approximately doubled when the session was increased from 3 hr to 6 hr under the 0.1 mg/kg unit dose. Increasing the unit dose to 0.2 mg/kg resulted in a decrease in the number of methamphetamine infusions earned (although the overall methamphetamine intake was slightly increased), likely reflecting an increase in the reinforcing efficacy of the higher unit dose (Yokel, 1987) (Fig. 3B).

Discrete choice tests: Despite the expected changes in methamphetamine self-administration behavior with increasing the session duration and the unit dose of the drug, the rats demonstrated a strong preference for the food, which increased from the 1^{st} choice session to the 5^{th} choice session (Fig. 3C), as indicated by a significant effect of Choice session, $F(4,28)=15.7$, $p<0.01$).

Exp. 3: Food versus methamphetamine preference during extended access (9 hr/day) to methamphetamine and food self-administration (Fig. 4–5)

Exp. 3a: Methamphetamine self-administration after food self-administration

Food and methamphetamine training: The rats increased their food and methamphetamine intake over days (Fig. 4B). The repeated measures ANOVA showed a significant effect of Session for both food [$F(5,75)=12.8$, $p<0.01$] and methamphetamine [$F(14,210)=34.4$, $p<0.01$].

Progressive ratio tests: Progressive ratio responding increased over time for both food and methamphetamine, an effect that was more pronounced for methamphetamine (Fig. 4C). The repeated measures ANOVA showed an approaching significant interaction between Session and Reward type [$F(2,30)=3.2$, $p=0.052$].

Discrete choice tests: Despite the higher "breaking point" for methamphetamine, the rats demonstrated a strong preference for the food, which increased over time (Fig. 4D). The statistical analysis of the preference score showed a significant effect of Choice session [$F(4,60)=7.1$, $p<0.01$].

Exp. 3b: Food self-administration after methamphetamine self-administration

Food and methamphetamine training: The rats increased their food and methamphetamine intake over days (Fig. 5B). The repeated measures ANOVA showed a significant effect of Session for both food [$F(14,56)=6.6$, $p<0.01$] and methamphetamine [$F(14,56)=18.1$, $p<0.01$].

Progressive ratio tests: Progressive ratio responding decreased for methamphetamine and increased for food over time (Fig. 5C) but because of the relatively small n (n=5), the interaction between Session and Reward type was not statistically significant [$F(2,8)=2.5$; $p=0.14$].

Discrete choice tests: As in Exp. 3a (and Exp. 1–2), the rats demonstrated a strong preference for food, which increased over time (Fig. 5D). The statistical analysis of the preference score showed a significant effect of Choice session [$F(4,16)=6.5$, $p<0.05$].

Correlations

In a final analysis, we combined the data for Exp. 3a and 3b to examine correlations (Pearson *r*) between escalation of methamphetamine intake (operationally defined as the change score of number of infusions on the last training day minus the number of infusions on the first training day), mean food-methamphetamine choice value and mean progressive ratio responding after we observed the escalation of methamphetamine self-administration (PR3 and C5 for Exp. 3a and PR1 and C1 for Exp. 3b, respectively). We found no correlations between choice and progressive ratio responding or the escalation measure ($r=0.14$, and $r=-0.35$, p values>0.1, respectively). In contrast, the correlations between progressive ratio responding and escalation was significant ($r=0.46$, $p=0.04$). [Note: we excluded one 'outlier' rat whose number of infusions on day 1 (94/9 hr) was >3 SD above the group mean].

Discussion

We used a discrete choice procedure to study palatable food versus methamphetamine preference in non-food deprived rats. We found that the rats preferred the palatable food over intravenous methamphetamine under different experimental conditions, including limited (3 hr/day) or extended (6–9 hr/day) access, alternate days or consecutive days of methamphetamine self-administration, and early or late (21 days) withdrawal periods. Additionally, two manipulations known to either increase methamphetamine seeking—drug priming (Gass et al., 2009; Schwendt et al., 2009)—or decrease the reward value of palatable foods—satiety (Dickinson et al., 1996)—did not reverse the food preference. We also found that neither progressive ratio responding (Hodos, 1961; Richardson and Roberts, 1996) nor escalation of drug self-administration under extended access conditions (9 hr/

day), a commonly used procedure to study compulsive drug use (Koob and Le Moal, 2001) were associated with methamphetamine preference.

Taken together, in agreement with previous cocaine studies (Ahmed, 2012), our data indicate that rats given access to intravenous methamphetamine and palatable food show persistent food preference. Our data suggesting higher reward value for food versus methamphetamine are also in agreement with the findings that under experimental conditions similar to those of Exp.3, food-trained rats are more resistant to punishment than methamphetamine-trained rats (Krasnova et al., 2014). Additionally, our data are in agreement with studies using behavioral economic analysis in rats showing overall higher reward values for palatable food versus cocaine or methamphetamine (Christensen et al., 2008; Galuska et al., 2011).

Methodological considerations and generality of the results

The main issue to consider is the degree to which our data generalize to other situations in which laboratory animals are given a choice between methamphetamine and food. To our knowledge, studies using discrete choice procedures were not performed with methamphetamine. However, based on the larger choice literature with cocaine, several experimental factors, including species, sex, the drug unit dose, the food type, the delay between lever pressing and reward delivery, may influence food-methamphetamine choice (Banks and Negus, 2012).

Regarding species, several studies have shown that monkeys will choose high cocaine unit doses over palatable food (Czoty and Nader, 2012; Negus, 2003; Paronis et al., 2002), a pattern of results that is different from the present results and previous studies (Ahmed, 2012). One consideration in the comparison between rat and monkey studies is the duration of drug self-administration training, typically shorter in rat studies. However, it is unlikely that the training duration is a critical factor in determining species differences in choice. Ahmed and colleagues have shown that preference for saccharin remained unchanged over several months of cocaine self-administration training (Ahmed, 2010, 2012). Furthermore, in ongoing studies in which we use our choice procedure to achieve long-term volitional (self-imposed) abstinence, we found no evidence for a shift in food-methamphetamine choice during extended drug self-administration training of 10 weeks in which some rats develop ‘addiction-like’ behavior in a rat addiction model (Deroche-Gamonet and Piazza, 2014). We also believe that it is unlikely that a methamphetamine unit dose higher than 0.1 or 0.2 mg/kg would shift food preference under our experimental conditions. These doses are on the descending limb of the dose response curve (Stefanski et al., 1999; Yokel and Pickens, 1973), and as demonstrated here and in previous studies, result in strong escalation of methamphetamine intake (Krasnova et al., 2014; Theberge et al., 2013). Additionally, manipulating the cocaine unit dose had minimal effect on saccharin preference (Lenoir et al., 2007). Finally, the higher ‘drug preference’ in monkeys, may reflect the fact that the alternative reward in monkey studies is not a highly palatable food, because these studies are designed to favor cocaine preference to study pharmacological mechanisms of cocaine preference (Ahmed, 2012). Thus, the higher cocaine preference in monkey studies might be due to the lower value of the food alternative in these studies.

There are also methodological considerations in interpreting the dissociation between progressive ratio responding for methamphetamine (which increased over time) and drug choice (which decreased over time). In this regard, while progressive ratio is commonly used as a measure of the drug reinforcing efficacy (Richardson and Roberts, 1996), in this procedure it is difficult to dissociate the drug's reinforcing effects from its reinforcement-independent "rate-altering" effects (e.g. increased locomotor activity) (Banks and Negus, 2012; Katz, 1990). We suspect that the reinforcing-independent effects of methamphetamine contributed to the dissociation between progressive ratio responding and choice.

A methodological parameter that might account for the low methamphetamine preference in our study is that we did not provide rats with sampling trials of palatable food and drugs prior to the mutually exclusive choice tests (Ahmed, 2012). However, it is unlikely that introducing sampling trials would have changed the results, because re-exposure to methamphetamine (priming) had no effect on our choice measure.

Another issue to consider is that our conclusions and those of other studies in which mutually exclusive discrete food-drug choice are used (Ahmed et al., 2013b) are different from those derived from studies using unlimited drug access (24 hr/day) in which the subjects have concomitant access to food (Bozarth and Wise, 1985; Chen et al., 2006; Johanson, 1975; O'Dell et al., 2007). Under those conditions, food intake decreases over time. A plausible explanation for this discrepancy is that decreased food intake is not due to decreases in the food 'value' but instead due to the direct pharmacological effects of psychostimulant drugs, which are known to decrease food intake (Sugrue, 1987).

A variable that we did not manipulate in our study was the rat's sex and therefore it is unknown whether our results generalize to females. This is an important issue, because many studies indicate that female are more sensitive than males to the behavioral effects of cocaine (Anker and Carroll, 2011; Becker and Hu, 2008; Carroll et al., 2004; Lynch, 2006). Additionally, recent choice studies indicate that a higher proportion of female rats prefer cocaine over food (Kerstetter et al., 2012; Perry et al., 2013). Finally, female rats self-administer more methamphetamine and escalate their drug intake faster than males (Reichel et al., 2012; Roth and Carroll, 2004).

Implications for "food addiction"

The original goal of our study was to determine whether we can use a food preference measure during extended methamphetamine self-administration to predict subsequent propensity to relapse using established relapse models (Bossert et al., 2013; Lu et al., 2004; Marchant et al., 2013). Our attempt was not successful because essentially all of our rats strongly preferred the palatable food independent of our different experimental conditions. This persistent food choice appears to support the controversial notion (Corsica and Pelchat, 2010; DiLeone et al., 2012) of 'food addiction' (Avena et al., 2008; Kenny, 2011).

In experimental animals, the notion of "food addiction" was derived from the observations that rats given extended access to palatable food demonstrated behavioral and physiological symptoms that mimic those observed after extended drug exposure (Avena et al., 2011; Avena et al., 2008). For example, rats given intermittent extended access to sugar solutions

or other palatable food demonstrate ‘binge-like’ intake patterns (Cifani et al., 2009; Colantuoni et al., 2001; Micioni Di Bonaventura et al., 2014) that are to some degree similar to the intake patterns observed after extended access to psychostimulant drugs (Pickens and Harris, 1968; Tornatzky and Miczek, 2000). Additionally, the binge-like pattern of both sugar intake or high-fat diet causes the development of opiate-like withdrawal symptoms (Colantuoni et al., 2002; Cottone et al., 2009). Finally, Johnson and Kenny (2010) demonstrated that withdrawal from extended high-fat diet causes deficits in brain stimulation reward that were significantly longer-lasting than those typically observed after withdrawal extended access to cocaine and other abuse drugs (Ahmed et al., 2002; Epstein and Shaham, 2010; Markou and Koob, 1991).

The strong food preference observed in our study, using an established extended access self-administration model thought to model compulsive drug use (George et al., 2014), and similar previous data of Ahmed and Lenoir (Ahmed, 2012) appear to support the notion of “food addiction” (Avena et al., 2008).

Concluding remarks

We demonstrated that laboratory rats strongly prefer palatable food pellets over intravenous methamphetamine, confirming previous studies using discrete choice procedures with intravenous cocaine. We also demonstrated that escalation of drug self-administration, a popular model of compulsive drug use, is not associated with a key feature of human addiction: reduced behavioral responding for non-drug rewards (O’Brien et al., 2006; Saunders, 2006).

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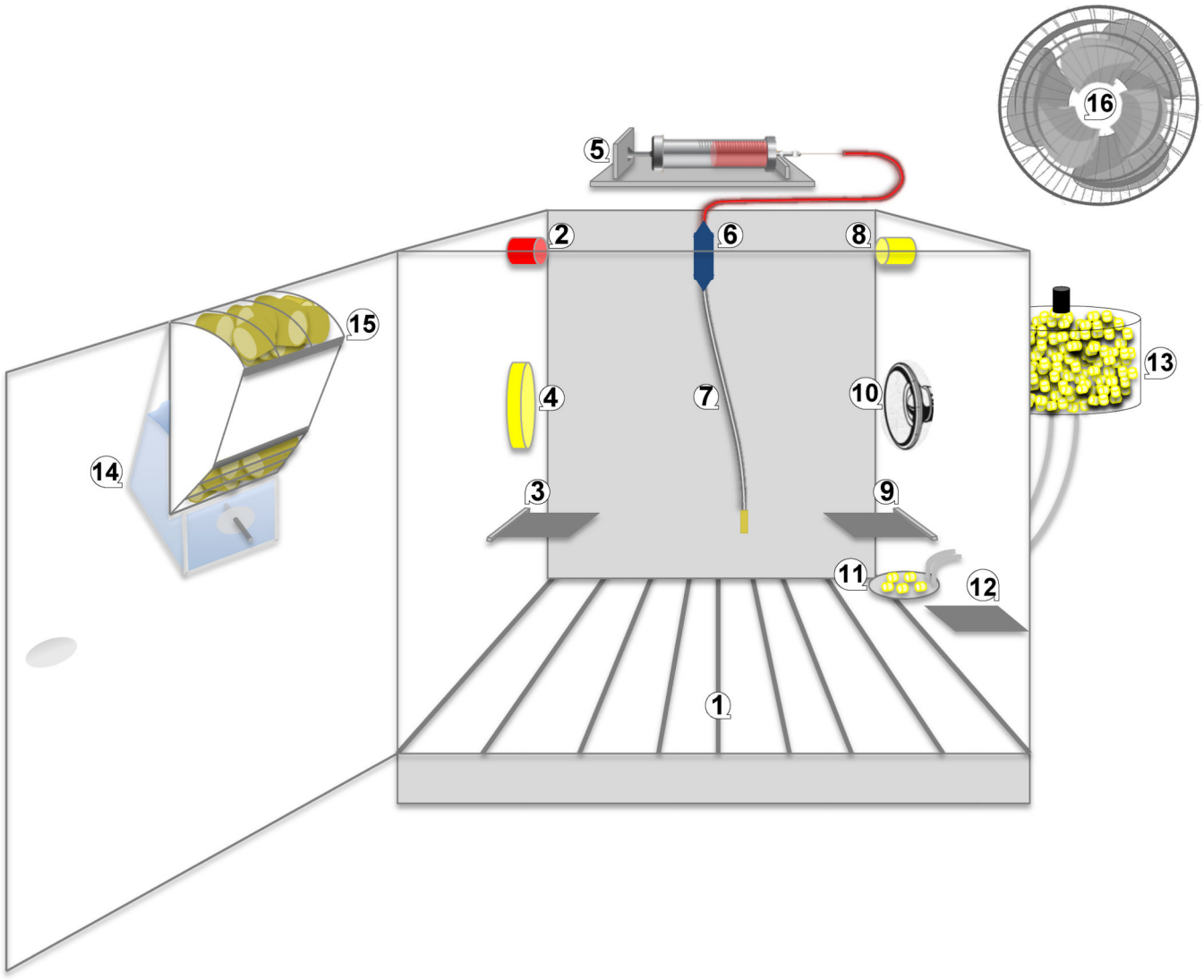

Figure 1. Apparatus

We equipped each chamber with a stainless steel grid floor (1) and two panels placed on the left and right walls. Left panel: Methamphetamine discriminative stimulus, red light (2), methamphetamine-paired active lever (retractable) (3), methamphetamine-paired cue light (4). We delivered the drug through an infusion pump (5) with a modified cannula (Plastics One) connected to a liquid swivel (6) via polyethylene-50 tubing that was protected by a metal spring (7). Right panel: Food discriminative stimulus, white light (8), food-paired active lever (retractable) (9), food-paired tone cue (10), food receptacle (11), and inactive (stationary) lever (12). We delivered food pellets through a food dispenser (13), connected by a rubber tube both located outside of the chamber. We placed a bottle of water (14) and a food hopper (15) on the external and internal side of the chamber's transparent polycarbonate door, respectively. We enclosed the apparatus inside a sound-attenuating cubicles fitted with a fan (16).

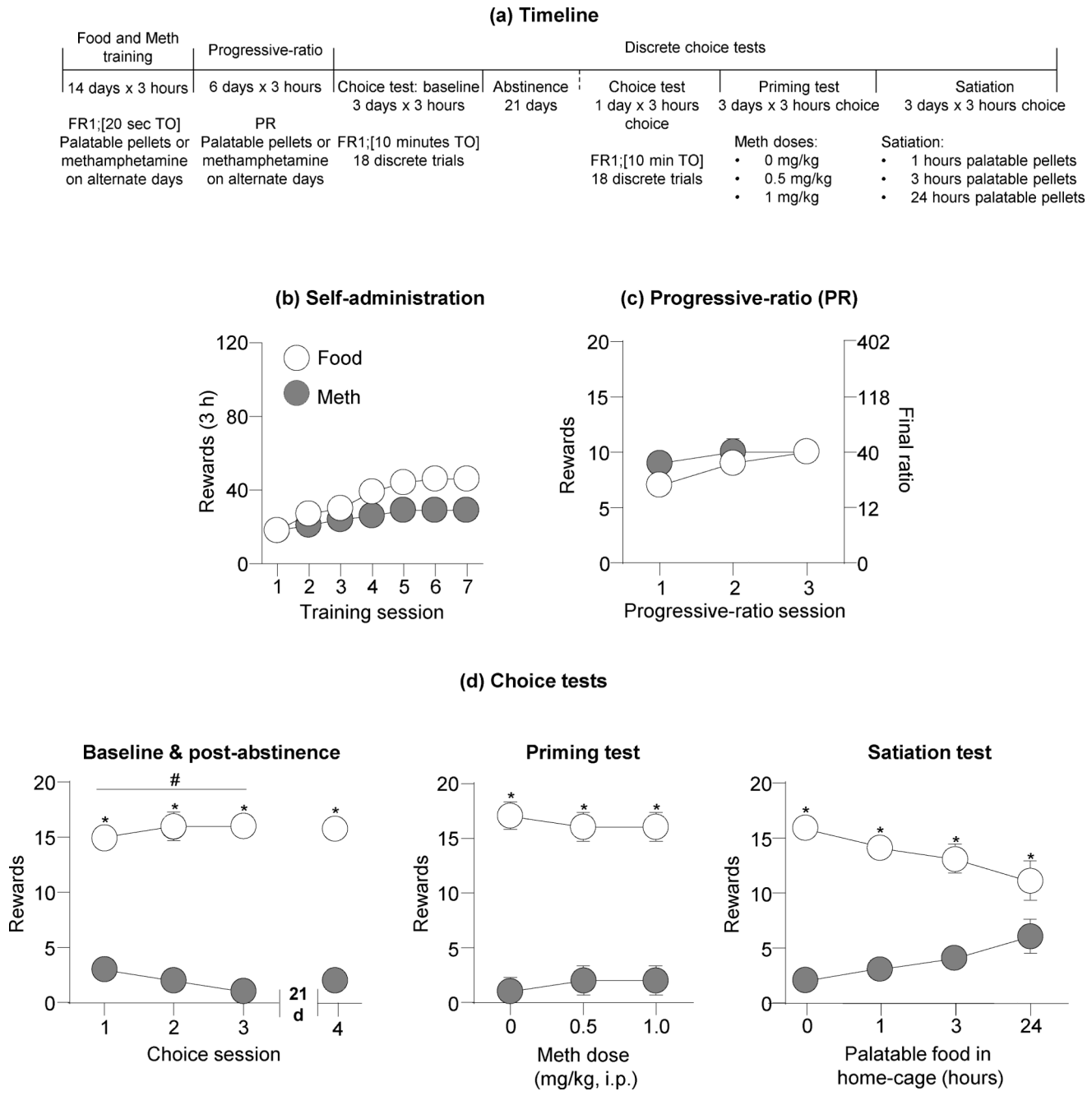

Figure 2. Palatable food preference after limited access (3 hr/day) to methamphetamine self-administration

(**A**) Timeline of the experiment. (**B**) Self-administration: Mean±SEM number of food rewards (5 palatable food pellets/reward delivery) or methamphetamine infusions (0.1 mg/kg/infusion) during the 3 hr sessions. (**C**) Progressive ratio tests: Mean±SEM of the final ratio completed for food reward or methamphetamine infusions. (**D**) Discrete choice tests: Mean±SEM of food reward and methamphetamine infusions earned during the choice sessions (18 trials every 10 min): Left: Initial choice sessions (baseline) and a choice session after 21 withdrawal days; Middle: Effect of methamphetamine priming on reward choice;

Right: Effect of increasing the duration of palatable pellets availability in the home cage on reward choice. * Different from the indifference level, $p<0.05$); # Different from the first session, $p<0.05$).

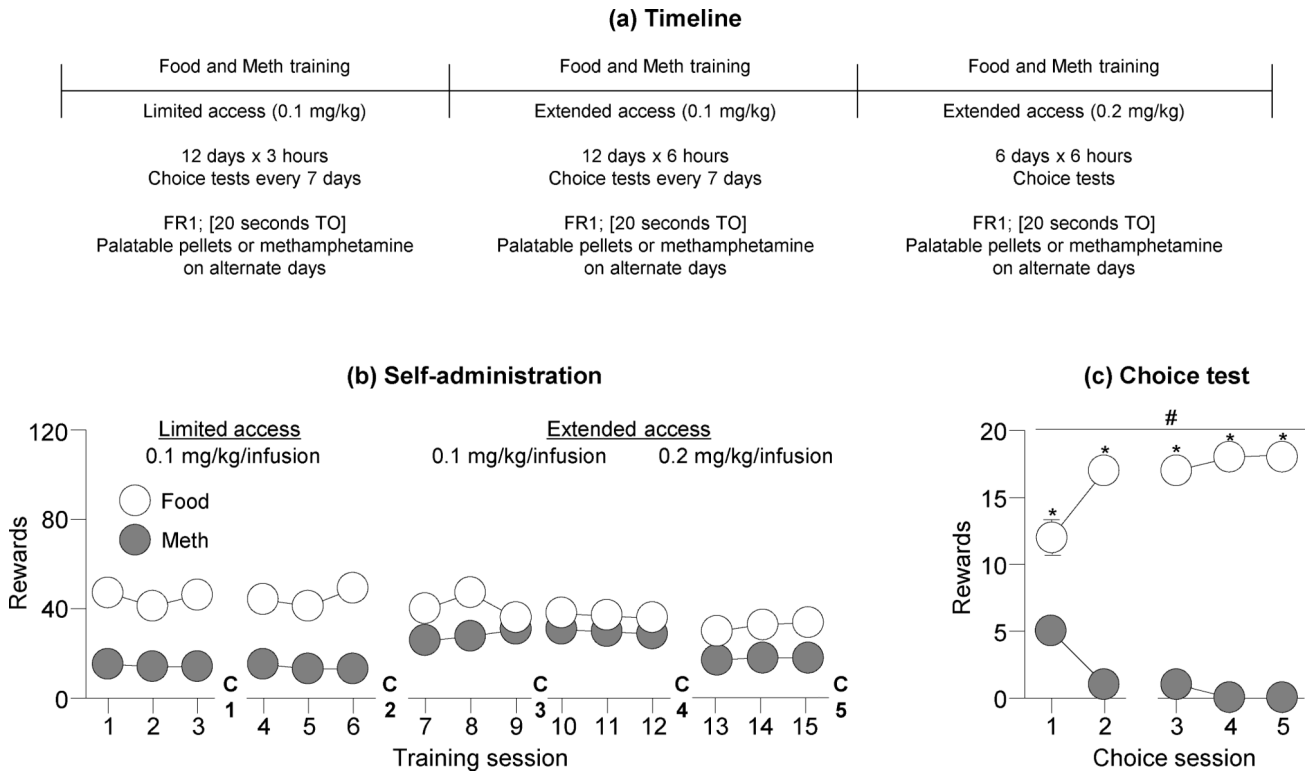

Figure 3. Palatable food preference during limited (3 hr/day) and extended access (6 hr/day) to methamphetamine self-administration

(**A**) Timeline of the experiment. (**B**) Self-administration: Mean±SEM number of food rewards (5 palatable food pellets/reward delivery) or methamphetamine infusions (0.1 or 0.2 mg/kg/infusion) during the alternate 3 hr/day and 6 hr/day training sessions(**C**) Discrete choice tests: Mean±SEM of food reward and methamphetamine infusions earned during the choice sessions (18 trials every 10 min). * Different from the indifference level, $p<0.05$. # Different from the first choice session, $p<0.01$).

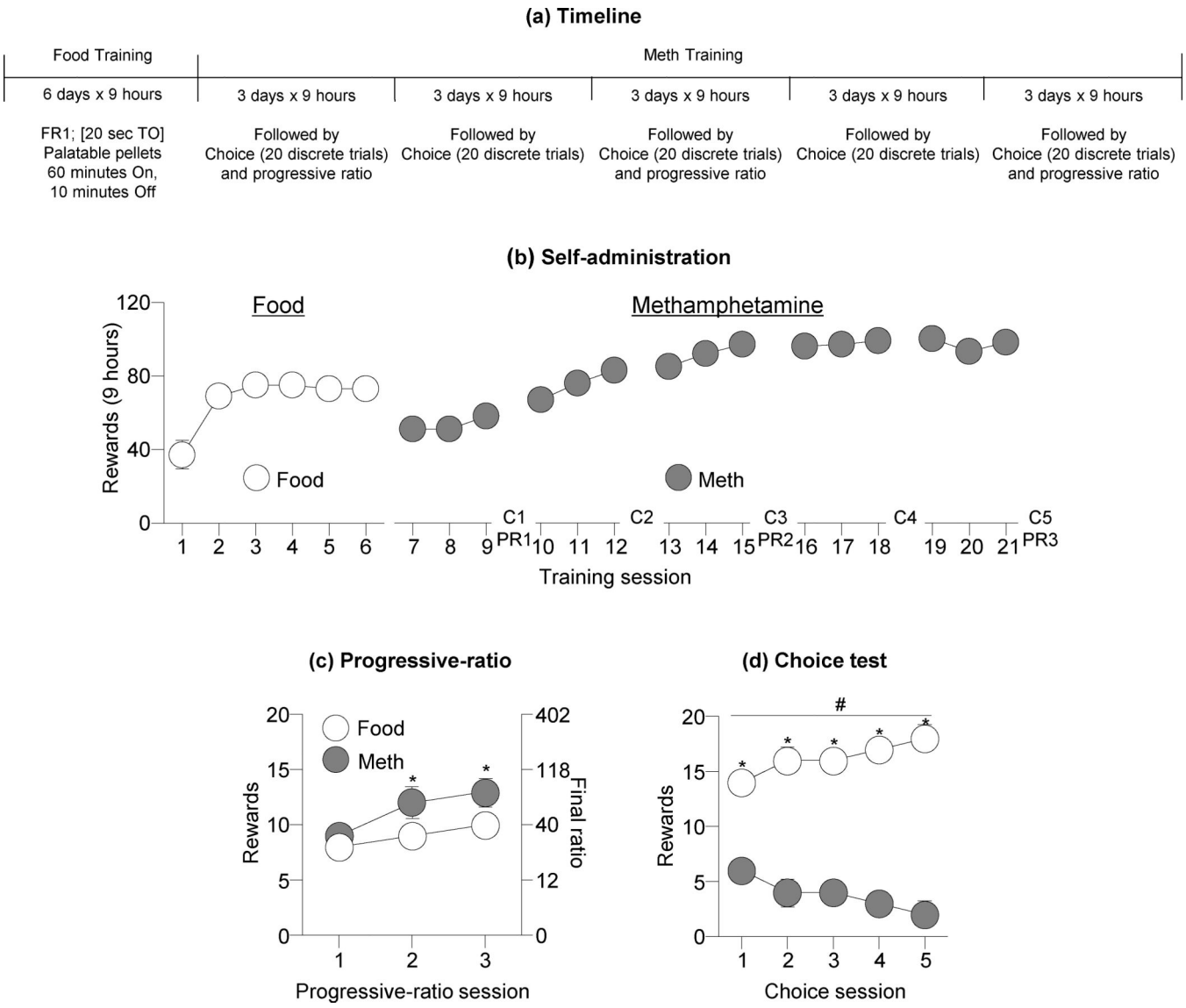

Figure 4. Strong food preference during extended access (9 hr/day) to methamphetamine self-administration

(**A**) Timeline of the experiment. (**B**) Self-administration: Mean±SEM number of food rewards (5 palatable food pellets/reward delivery) or methamphetamine infusions (0.1 mg/kg/infusion) during the 9 hr sessions. (**C**) Progressive ratio tests: Mean±SEM of the final ratio completed for food reward or methamphetamine infusions. (**D**) Discrete choice tests: Mean±SEM of food reward and methamphetamine infusions earned during the choice sessions (20 trials every 10 min) * Different from the indifference level, $p<0.05$. # Different from the first session, $p<0.01$).

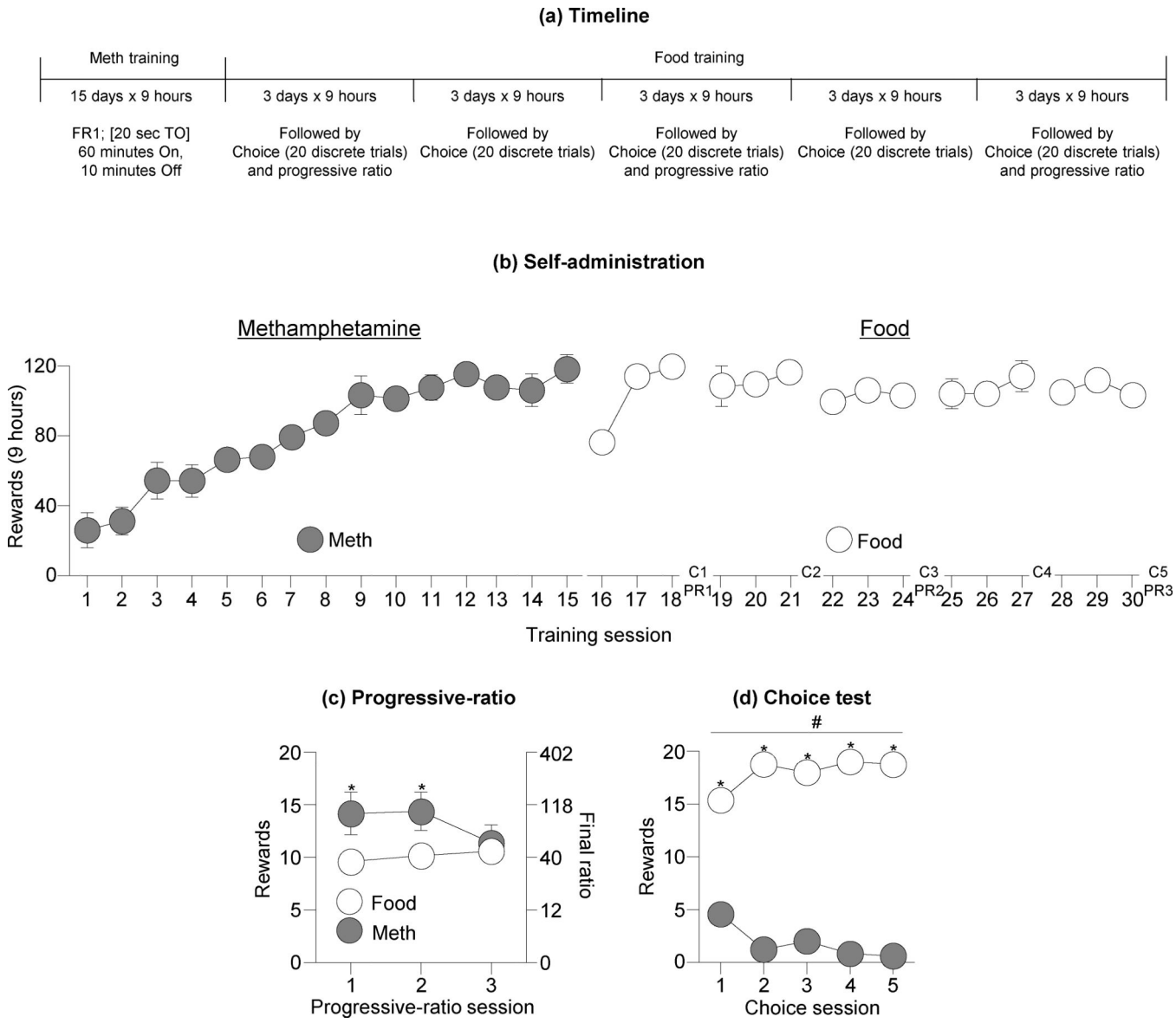

Figure 5. Strong food preference after reversal of the training conditions (9 hr/day sessions)

(**A**) Timeline of the experiment. (**B**) Self-administration: Mean±SEM number of food rewards (5 palatable food pellets/reward delivery) or methamphetamine infusions (0.1 mg/kg/infusion) during the 9 hr sessions. (**C**) Progressive ratio tests: Mean±SEM of the final ratio completed for food reward or methamphetamine infusions. (**D**) Discrete choice tests: Mean±SEM of food reward and methamphetamine infusions earned during the choice sessions (20 trials every 10 min). * Different from the indifference level, $p<0.05$). # Different from the first session ($p<0.001$).