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Rats have low motivation to self-administer oral methamphetamine across increasing response requirements

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Abstract

Methamphetamine (METH) is a psychostimulant drug that has become increasingly popular in recent years, with overdose deaths more than doubling during the second half of the 2010s. As methamphetamine use disorder rates continue to increase, finding effective treatment strategies to decrease METH dependence is important. Animal studies are well-suited for studying the neurobiological mechanisms underlying addiction-like behaviors. Although individuals can ingest METH orally, few studies have examined oral METH self-administration in animals. Mice show decreased responding for oral METH as the response requirement increases across sessions. The purpose of the current study was to determine if rats show a similar decrease in motivation to earn oral METH across increasing response requirements. Sixteen Sprague Dawley rats were trained to emit a response in an aperture to receive a 0.1-ml METH solution (40 mg/l) according to an FR 1 schedule. The FR requirement increased across sessions to a terminal FR 10. Responses for METH decreased significantly when an FR 10 schedule was used. These results suggest that rats, similarly to mice, have low motivation to self-administer oral METH.

Keywords

methamphetamine; oral self-administration; motivation; reinforcer efficacy; addiction; rat

Methamphetamine (METH) is a psychostimulant drug that can be prescribed to treat attention-deficit hyperactivity disorder. However, between 2015 and 2019, recreational METH use increased 43%, and the number of individuals diagnosed with a METH use disorder (MUD) increased 62%; more alarmingly, the number of overdose deaths attributed,

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at least partially, to psychostimulants (primarily METH) increased 180% [1]. Given the recent increase in METH use, there is a pressing need to understand the neurobiological mechanisms that underly METH dependence. Animal research is valuable for elucidating genetic [2], neurobiological [3], cognitive-behavioral [4,5], and/or socioenvironmental [6] determinants of METH dependence-like behavior.

Preclinical studies can measure distinct aspects of addiction by using drug self-administration tasks. Although rodents are often trained to self-administer METH via the intravenous route, recent studies have successfully used an oral solution containing METH as a reinforcer [7–11]. However, when the response requirement increases across sessions, the number of responses for METH decreases precipitously [7,9]. This pattern of responding contrasts with what is typically observed when stimulants are delivered intravenously [12,13]. The one study to test oral METH self-administration in rats used low response requirements (fixed ratio [FR] 1 and FR 2) [8], which does not allow one to test the reinforcing efficacy of a drug. Therefore, the goal of the present study was to determine if rats will continue responding for oral METH across increasing response requirements.

Sixteen Sprague Dawley rats (eight of each sex) arrived from Envigo (Indianapolis, IN) at postnatal day (PND) 38 (males) or PND 45 (females) and were placed in a climate- and humidity-controlled room maintained on a 12:12-h reverse light/dark cycle (lights off at 700 h). Rats were pair housed in cages that have been previously described [14]. Rats had *ad libitum* access to food and water during the experiment. All experimental procedures were carried out according to the Current Guide for the Care and Use of Laboratory Animals [15] under a protocol approved by the Northern Kentucky University Institutional Animal Care and Use Committee (Protocol #2022–01-22). Behavioral testing occurred during the dark phase, with sessions beginning approximately between 1130–1430 h. Rats were previously trained in an operant procedure to measure risky decision making and received four subcutaneous injections of METH (0, 0.25, 0.5, and 1.0 mg/kg; one injection of each dose). Four rats also received a single injection of METH (2.0 mg/kg). Injections of METH occurred from PND 144 (male)/151 (female) to PND 153 (male)/160 (female), with each injection occurring once every three days. For four rats, the last injection occurred on PND 156 (male) or PND 163 (female).

METH self-administration occurred in 16 MED Associates operant conditioning chambers that have been previously described [14]. Relevant to the current experiment, a liquid receptacle (5.08 × 5.08 cm; product ENV-200R3BM) was positioned 2 cm above the floor in the bottom-center of the back wall between two nose poke apertures (2.54 × 2.14 cm; ENV-114BM) that were located 1.43 cm above the floor (measured from bottom of aperture). Two audio speakers (ENV-224AM-3) connected to sound generators (ENV-230) were added to the front wall located 11.1 cm above the floor.

Beginning at PND 166 (males) or PND 173 (females), rats were trained to self-administer sucrose (10%) according to an FR 1 schedule of reinforcement for three sessions. Each session began with illumination of a house light located at the top-center of the back wall and illumination of the active aperture. For half of the rats, a response in the left aperture led to an infusion of sucrose (0.1 ml across 5.9 s). Completing the response requirement

resulted in reinforcer delivery paired with a 2-s presentation of a 5 kHz tone emitted from both speakers. A 14.1-s time out was imposed following each sucrose delivery. The aperture light was extinguished during reinforcer delivery and during the time out. Sessions ended after rats earned 20 infusions or after 1 h.

Rats were trained to self-administer METH (20 mg/l) mixed in 8.5% sucrose for one session. For the next four sessions, rats self-administered METH (40 mg/l) mixed in decreasing concentrations of sucrose (6.5, 4.5, 2.5, 0.5%; one session for each concentration). Once the sucrose concentration reached 2.5%, the 20-infusion limit was removed. During the last two training sessions (METH mixed with 2.5% and 0.5% sucrose), males emitted 55.00 (± 10.82) and 38.75 (± 8.71) responses on the active aperture and 20.50 (± 4.45) and 16.00 (± 3.57) responses on the inactive aperture. Females did not significantly differ in number of active (59.38 ± 7.85 and 54.88 ± 7.90) or inactive (20.75 ± 4.450 and 17.25 ± 5.00) responses relative to males (no main effect of sex; no significant interactions involving sex, F's ≤ 2.68, p's ≥ .12, η_p^2's ≤ .16).

Rats self-administered METH (40 mg/l) mixed in distilled water (no sucrose added) according to an FR 1 schedule for five sessions. The response requirement increased to an FR 3 for three sessions, followed by an FR 5 (four sessions) and an FR 10 (eight sessions).

Active and inactive aperture responses were analyzed with an ANOVA, with aperture, session, and sex as factors. Separate ANOVAs were performed for each response requirement. Total infusions were analyzed with an ANOVA, with session and sex as factors. To directly compare the number of active and inactive responses across each FR requirement, responses on the active and the inactive aperture were averaged across the final two sessions of each response requirement before being analyzed with an ANOVA, with response requirement, aperture, and sex as factors. Infusions were analyzed with an ANOVA, with response requirement and sex as factors. Statistical significance was defined as $p < .05$. When the assumption of sphericity was violated, Greenhouse-Geisser-corrected degrees of freedom were used. Partial eta squared was used as measure of effect size, with effect sizes of .01, .06, and .14 indicating small, moderate, and large effect sizes, respectively [16].

Across each response requirement, active responses were higher than inactive responses, F's ≥ 25.17, p's < .01, η^2_p's ≥ .64 (Fig. 1a). When an FR 1, an FR 3, and an FR 5 schedule were in effect, females responded more on both the active and the inactive aperture compared to males, F's ≥ 5.07, p's ≤ .04, η^2_p's ≥ .27. When an FR 1 and an FR 10 schedule was used, responses on the active and the inactive apertures decreased across sessions, F's ≥ 4.90, p's ≤ .01, η^2_p's ≥ .26. Under an FR 3 schedule, there was a decrease in active, but not inactive, responses from the first session to the second session, $F(1.30, 18.20) = 7.41$, $p < .01$, $\eta^2_p = .35$.

Females earned more infusions of METH when an FR 5 schedule was used, $F(1, 14) = 4.78$, $p = .05$, $\eta^2_p = .25$ (Fig. 1b). The number of infusions decreased across sessions when the FR 1, the FR 3, and the FR 10 schedules were used, F's ≥ 4.03, p's ≤ .01, η^2_p's ≥ .22.

When active and inactive responses were averaged across the final two sessions of each response requirement, there were main effects of response requirement (FR 10 < all other schedules), aperture (active > inactive), and sex (female > male), F's ≥ 5.70, p's ≤ .03, η^2_p's ≥ .29 (Fig. 1c). Active responses were lower when an FR 10 was used compared to all other schedules; likewise, inactive responses were lower when an FR 10 was used compared to an FR 1 and an FR 5 (response requirement × aperture interaction: $F(3, 42) = 3.97$, $p = .01$, $\eta^2_p = .22$). Responses, collapsed across active and inactive apertures, were lower for females, but not males, when an FR 10 schedule was used compared to the other schedules of reinforcement (response requirement × sex interaction; $F(3, 42) = 2.95$, $p = .04$, $\eta^2_p = .17$).

As with the number of active and inactive aperture responses, infusions decreased as the response requirement increased, $F(1.14, 15.90) = 44.77$, $p < .01$, $\eta^2_p = .76$, and females earned more infusions than males, $F(1, 14) = 6.55$, $p = .02$, $\eta^2_p = .32$ (Fig. 1d). The significant response requirement × sex interaction, $F(1.14, 15.90) = 6.21$, $p = .02$, $\eta^2_p = .31$, can be attributed to the sharper decline in infusions earned for females across response requirements compared to males.

Because the dose delivered with each infusion differed across each sex (~.009 mg/kg/infusion for males and ~0.016 mg/kg/infusion for females), we modified the experiment such that each rat earned the same dose of METH (0.01 mg/kg/infusion). Rats received 10 sessions in which they self-administered saccharin (1%). Rats then self-administered METH (0.01 mg/kg/infusion) mixed with decreasing concentrations of saccharin: 1% (nine sessions), 0.8% (six sessions), 0.4% (four sessions), 0% (10 sessions). During each session, responses were reinforced according to an FR 1 schedule of reinforcement. Rats received an additional 11 sessions in which responses for METH (0.01 mg/kg/infusion) were reinforced according to an FR 2 schedule of reinforcement. These data were analyzed similarly to what was described above, except the number of infusions averaged across the final two sessions of the FR 1 and the FR 2 phase of METH self-administration were analyzed only.

Active responses were higher than inactive responses across each phase of the experiment, F's ≥ 11.32, p's ≤ .01, η^2_p's ≥ .45 (Fig. 2a). Active, but not inactive, responses increased across sessions when saccharin was delivered in the absence of METH (session × aperture interaction: $F(3.01, 42.09) = 17.79$, $p < .01$, $\eta^2_p = .56$), but responses decreased across each phase that METH was used as the reinforcer (main effect of session: F's ≥ 4.20, p's ≤ .02, η^2_p's ≥ .23. Sex differences were observed when saccharin was delivered in the absence of METH only, with females responding more than males on both the active and the inactive apertures, $F(1, 14) = 4.65$, $p = .05$, $\eta^2_p = .25$. Although there was a session × sex interaction during METH/saccharin (1%) self-administration, $F(3.11, 43.50) = 3.10$, $p = .04$, $\eta^2_p = .18$, Tukey's post hoc tests did not reveal any significant differences between sex.

Figure 2b shows active and inactive responses averaged across the final two sessions of each phase of the experiment. There were main effects of phase (responses decreased as saccharin concentration decreased), $F(2.44, 34.14) = 18.05$, $p < .01$, $\eta^2_p = .56$, and aperture (active > inactive), $F(1, 14) = 48.97$, $p < .01$, $\eta^2_p = .78$. Inactive responses did not vary across experimental phase, but active responses were highest when saccharin (1%) was delivered

in the absence of METH and were significantly lower when METH was delivered in the absence of saccharin, $F(1.82, 25.42) = 13.97$, $p < .01$, $\eta^2_p = .50$. Tukey's post hoc tests also showed that active responses were higher than inactive responses when saccharin was added to METH (p's ≤ .05), but active responses did not significantly differ from inactive responses when saccharin was removed from the METH solution (p's ≥ .96). Rats earned more infusions of METH (0.01 mg/kg/infusion) when an FR 1 schedule was used compared to an FR 2 schedule, $F(1, 14) = 10.07$, $p < .01$, $\eta^2_p = .42$ (Fig. 2c). Because the number of infusions decreased from an FR 1 to an FR 2, we did not increase the response requirement further.

Oral operant drug self-administration is commonly used to measure the reinforcing effects of ethanol [17], although animals will self-administer other drugs delivered orally, including fentanyl [18], cocaine [19], and METH [7–11]. Experiments measuring oral self-administration of psychostimulants have primarily used low response requirements (FR 1 – FR 10). When the response requirement to earn oral METH increases, mice emit fewer responses [7,9; but see 11 for increased responses as response requirement increases to an FR 5]. The current results corroborate what has been observed with mice; that is, oral METH has low reinforcing efficacy in rats. One potential explanation for the current results is METH's bitter taste. Although we did not quantify how much liquid solution each rat consumed, we often noticed that rats left the METH solution in the liquid well, something we rarely noticed during sucrose or saccharin self-administration.

Concerning sex differences, we found that females earned more METH infusions compared to males when low response requirements were used. Epidemiological studies indicate that men are more likely to use METH [20]; however, preclinical studies examining drug selfadministration report mixed results, with some studies finding increased METH intake in males [21] and others showing increased intake in females [22; see 23 for a comprehensive review]. In the current study, the increased self-administration observed in females is qualified by their increased inactive responses. Additionally, when we adjusted the dose of METH to control for weight differences (40 mg/l to 0.01 mg/kg/infusion), we did not observe significant differences in METH infusions between males and females. If one is interested in examining sex differences in addiction vulnerability, we recommend using a drug dose that will account for weight differences across sex.

The results of this study highlight one potential limitation of using the oral route of administration when measuring METH self-administration. This route of administration may not be well-suited to measure motivation to consume METH. However, we must note that studies using this route have made important contributions concerning METH dependence-like behavior. Mice that consume more METH have a hyperactive glutamatergic system in the nucleus accumbens [11], and female rats exposed to nicotine early in life (PND 25–34) self-administer more METH compared to sex-matched controls and treatment-matched males [8]. The latter finding suggests that females that use nicotine-containing products during adolescence may be more sensitive to the reinforcing effects of METH later in life, thus increasing the probability of developing a MUD. Given that Harmony et al. [8] used the same METH concentration [40 mg/l] for males and females, this finding needs to be

interpreted with some caution as the sex differences reported could result from females receiving a functionally higher dose of METH relative to males.

Although more work is needed to optimize oral self-administration of METH, this route of administration provides some advantages to researchers. First, there is no need for surgical intervention as with intravenous drug self-administration. This can allow researchers to examine drug self-administration in a shorter period as animals do not need time to recover from surgery. As noted previously [8], this better enables one to measure drug self-administration during the short adolescent period (approximately 2–5 weeks). Furthermore, the probability of attrition is lower as there is no risk of losing subjects due to complications resulting from surgical intervention or loss of catheter patency. Thus, using the oral route of administration may be useful for measuring other aspects of addiction-like behavior, such as compulsive drug seeking [18] or reinstatement of drug seeking [8].

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References

[1]. Han B, Compton WM, Jones CM, Einstein EB, Volkow ND, Methamphetamine use, methamphetamine use disorder, and associated overdose deaths among US adults, JAMA Psychiatry 78 (2021) 1329–1342. 10.1001/jamapsychiatry.2021.2588. [PubMed: 34550301]

[2]. Stafford AM, Reed C, Baba H, Walter NA, Mootz JR, Williams RW, Neve KA, Fedorov LM, Janowsky AJ, Phillips TJ, *Taar1* gene variants have a causal role in methamphetamine intake and response and interact with *Oprm1*, Elife 8 (2019) e46472. 10.7554/eLife.46472. [PubMed: 31274109]

[3]. Cordie R, McFadden LM, Optogenetic inhibition of the medial prefrontal cortex reduces methamphetamine-primed reinstatement in male and female rats, Behav. Pharmacol 30 (2019) 506–513. 10.1097/FBP.0000000000000485. [PubMed: 31033525]

[4]. Istin M, Thiriet N, Solinas M, Behavioral flexibility predicts increased ability to resist excessive methamphetamine self-administration, Addict. Biol 22 (2017) 958–966. 10.1111/adb.12384. [PubMed: 26969296]

[5]. Taylor SB, Watterson LR, Kufahl PR, Nemirovsky NE, Tomek SE, Conrad CD, Olive MF, Chronic variable stress and intravenous methamphetamine self-administration - Role of individual differences in behavioral and physiological reactivity to novelty, Neuropharmacology 108 (2016) 353–363. 10.1016/j.neuropharm.2016.05.003. [PubMed: 27163191]

[6]. Nicolas C, Hofford RS, Dugast E, Lardeux V, Belujon P, Solinas M, Bardo MT, Thiriet N, Prevention of relapse to methamphetamine self-administration by environmental enrichment: involvement of glucocorticoid receptors, Psychopharmacology 239 (2022) 1009–1018. 10.1007/s00213-021-05770-6. [PubMed: 33768375]

[7]. Fultz EK, Martin DL, Hudson CN, Kippin TE, Szumlinski KK, Methamphetamine-alcohol interactions in murine models of sequential and simultaneous oral drug-taking, Drug Alcohol Depend. 177 (2017) 178–186. 10.1016/j.drugalcdep.2017.03.026. [PubMed: 28601731]

[8]. Harmony ZR, Alderson EM, Garcia-Carachure I, Bituin LD, Crawford CA, Effects of nicotine exposure on oral methamphetamine self-administration, extinction, and drug-primed reinstatement in adolescent male and female rats, Drug Alcohol Depend. 209 (2020) 107927. 10.1016/j.drugalcdep.2020.107927. [PubMed: 32106019]

[9]. Honeywell KM, Van Doren E, Szumlinski KK, Selective inhibition of PDE4B reduces methamphetamine reinforcement in two C57BL/6 substrains, Int. J. Mol. Sci 23 (2022) 4872. 10.3390/ijms23094872. [PubMed: 35563262]

[10]. Shabani S, Dobbs LK, Ford MM, Mark GP, Finn DA, Phillips TJ, A genetic animal model of differential sensitivity to methamphetamine reinforcement, Neuropharmacology 62 (2012) 2168–2176. 10.1016/j.neuropharm.2012.01.002.

[11]. Szumlinski KK, Lominac KD, Campbell RR, Cohen M, Fultz EK, Brown CN, Miller BW, Quadir SG, Martin D, Thompson AB, von Jonquieres G, Klugmann M, Phillips TJ, Kippin TE, Methamphetamine addiction vulnerability: the glutamate, the bad and the ugly, Biol. Psychiatry 81 (2017) 959–970. 10.1016/j.biopsych.2016.10.005. [PubMed: 27890469]

[12]. Wong WC, Marinelli M, Adolescent-onset of cocaine use is associated with heightened stress-induced reinstatement of cocaine seeking, Addict. Biol 21 (2016) 634–645. 10.1111/adb.12284. [PubMed: 26202521]

[13]. Diergaarde L, Pattij T, Poortvliet I, Hogenboom F, de Vries W, Schoffelmeer ANM, De Vries TJ, Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats, Biol. Psychiatry 63 (2008) 301–308. 10.1016/j.biopsych.2007.07.011. [PubMed: 17884016]

[14]. Yates JR, Horchar MJ, Ellis AL, Kappesser JL, Mbambu P, Sutphin TG, Dehner DS, Igwe HO, Wright MR, Differential effects of glutamate N-methyl-D-aspartate receptor antagonists on risky choice as assessed in the risky decision task, Psychopharmacology 238 (2021) 133–148. 10.1007/s00213-020-05664-z. [PubMed: 32936321]

[15]. National Research Council, Guide for the Care and Use of Laboratory Animals, eighth ed., Washington, DC., 2011, 10.17226/12910.

[16]. Cohen J, Statistical Power Analysis for the Behavioral Sciences, second ed., Lawrence Erlbaum Associates, Hillsdale, NJ, 1988.

[17]. Vena AA, Zandy SL, Cofresi RU, Gonzalez RA, Behavioral, neurobiological, and neurochemical mechanisms of ethanol self-administration: a translational review, Pharmacol. Ther 212 (2020) 107573. 10.1016/j.pharmthera.2020.107573. [PubMed: 32437827]

[18]. Monroe SC, Radke AK, Aversion-resistant fentanyl self-administration in mice, Psychopharmacology 238 (2021) 699–710. 10.1007/s00213-020-05722-6. [PubMed: 33226446]

[19]. DePoy LM, Allen AG, Gourley SL, Adolescent cocaine self-administration induces habit behavior in adulthood: sex differences and structural consequences, Trans. Psychiatry 6 (2016) e875. 10.1038/tp.2016.150.

[20]. Jones CM, Compton WM, Mustaquim D, Patterns and characteristics of methamphetamine use among adults - United States, 2015–2018, Morb. Mortal. Wkly. Rep 69 (2020) 317–323. 10.15585/mmwr.mm6912a1.

[21]. Daiwile AP, Jayanthi S, Ladenheim B, McCoy MT, Brannock C, Schroeder J, Cadet JL, Sex differences in escalated methamphetamine self-administration and altered gene expression associated with incubation of methamphetamine seeking, Int. J. Neuropsychopharmacol 22 (2019). 10.1093/ijnp/pyz050.

[22]. Reichel CM, Chan CH, Ghee SM, See RE, Sex differences in escalation of methamphetamine self-administration: cognitive and motivational consequences in rats, Psychopharmacology 223 (2012). 10.1007/s00213-012-2727-8.

[23]. Daiwile AP, Jayanthi S, Cadet JL, Sex differences in methamphetamine use disorder perused from pre-clinical and clinical studies: potential therapeutic impacts, Neurosci. Biobehav. Rev 137 (2022) 104674. 10.1016/j.neubiorev.2022.104674. [PubMed: 35452744]

Research Highlights

- Responses for oral METH decrease when an FR 10 schedule is used
- Females earn more METH (40 mg/l) but also respond more on inactive aperture
- Sex differences disappear when METH (0.01 mg/kg/infusion) is used

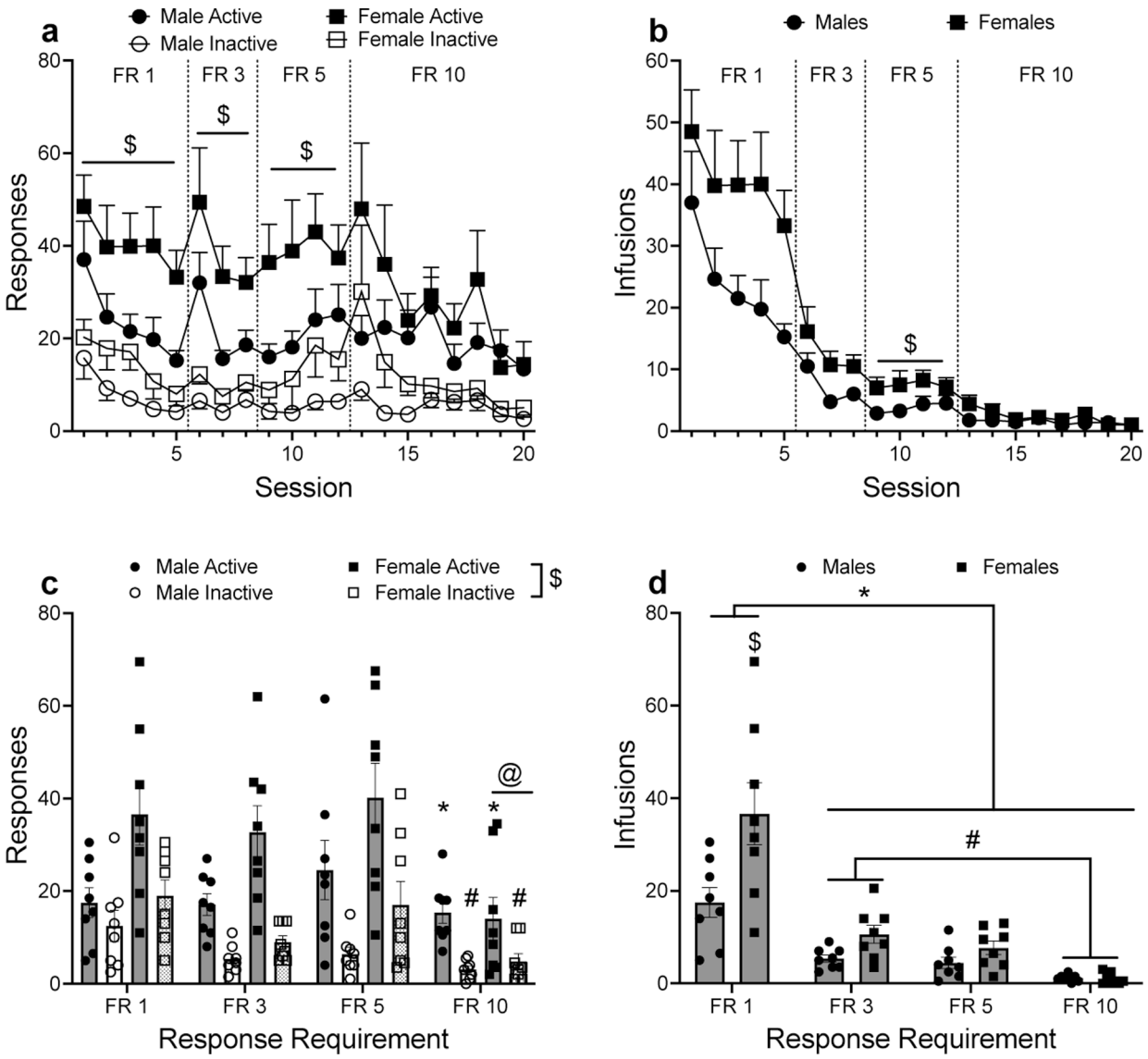

Figure 1.

Mean (±SEM) responses on the active and the inactive aperture (**a**) and number of infusions (**b**) across increasing response requirements. Mean (±SEM) responses on the active and the inactive aperture (**c**) and number of infusions (**d**) averaged across the final two sessions of each response requirement. $$p < .05$, compared to males. *$p < .05$, compared to all other FRs. #$p < .05$, FR 10 compared to FR 1 and FR 5 (panel **c**) or to FR 3 (panel **d**). @$p < .05$, compared to all other FRs.

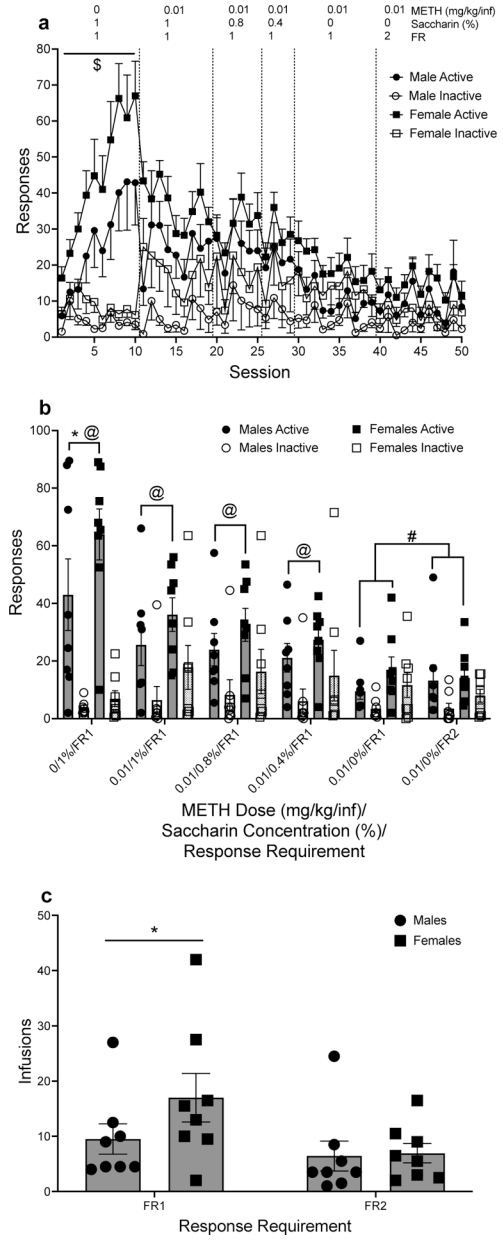

Figure 2.

Mean (±SEM) responses on the active and the inactive aperture across different phases of METH (0.01 mg/kg/infusion) self-administration (**a**) and averaged across the final two sessions of each phase (**b**). Mean (±SEM) number of infusions averaged across the final two sessions of METH self-administration when an FR 1 or an FR 2 schedule were used. $\$p < .05$, compared to males. $*p < .05$, compared to all other phases of drug self-administration (panel **b**) or to the FR 2 schedule (panel **c**). $@p < .05$, relative to the inactive aperture. $\#p < .05$, compared to METH/saccharin solutions.