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Abstract

Depression and psychostimulant addiction are co-morbid conditions; depression is a significant risk factor for psychostimulant abuse, and the rate of depression in drug addicts is higher than in the general population. Despite the prevalence of this comorbidity, there are few animal models examining psychostimulant abuse behaviors in depression. We have shown previously that while rats selectively bred for depression-like phenotypes (SwLo) have blunted mesolimbic dopamine (DA) signaling and locomotor responses to dopaminergic drugs, they voluntarily administer excessive amounts of psychostimulants compared to normal or depression-resistant (SwHi) rats in oral consumption paradigms. To determine whether this increased drug intake by depression-sensitive rats extends to operant self-administration, we assessed fixed ratio-1, progressive ratio, extinction, and reinstatement responding for cocaine and amphetamine in SwLo and SwHi rats. Contrary to the oral consumption results, we found that the SwHi rats generally responded more for both cocaine and amphetamine than the SwLo rats in several instances, most notably in the progressive ratio and reinstatement tests. Food-primed reinstatement of food seeking was also elevated in SwHi rats. These results provide further insight into the neurobiology of depression and addiction comorbidity and caution that oral and operant psychostimulant self-administration paradigms can yield different, and this case, opposite results.

1. Introduction

1.1. Addiction and depression comorbidity

High rates of depression in cocaine abusers were first reported over 20 years ago (Weiss *et al.*, 1986), and experience in drug abuse clinics has continued to support an association between psychiatric disorders and substance abuse (Kilbey *et al.*, 1992). In general, cocaine

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Conflict of Interest

DW is co-inventor on a patent concerning the use of selective DBH inhibitors for the treatment of cocaine dependence (US-2010-015748-A1; “Methods and Compositions for Treatment of Drug Addiction”). The other authors declare no conflicts of interest.

abuse and dependence are associated with increased risk for depression, with lifetime rates of major depression ranging from 25%–61% in cocaine abusers versus ~10% for community control populations (Rounsaville, 2004). The likelihood of substance abuse/dependence disorders and depression to occur together in the same individuals is ~ 5 times greater than would be expected by the prevalence of each disorder alone, though the complex factors contributing to this comorbidity remain a matter for debate (Grant, 1995, Regier *et al.*, 1990, Rounsaville, 2004, Volkow, 2004).

1.2. The self-medication hypothesis

One of the leading theories to explain depression and drug addiction comorbidity is the "self-medication hypothesis", stemming from common risk factors and similarities in the neurobiology of depression and drug dependence. This theory posits that individuals with underlying depression have deficits in brain reward systems and may turn to drugs that create euphoric feelings to compensate for their intrinsic anhedonia and motivational deficiencies (Markou *et al.*, 1998). The mesolimbic dopamine (DA) system, particularly the DA neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc), is a critical neural substrate for the rewarding and reinforcing effects of psychostimulant drugs of abuse (Bardo, 1998, Feltenstein and See, 2008, Leshner and Koob, 1999, Leyton, 2007). Furthermore, there appears to be an association between reduced DA function and depression because key symptoms associated with major depression, such as anhedonia, are consistent with a hypofunctioning DA reward system (Markou *et al.*, 1998, Nestler and Carlezon, 2006, Weiss *et al.*, 1986).

1.3. SwLo rats as a model of addiction and depression comorbidity

We have shown previously that SwLo rats selectively bred for low activity in the forced swim test model of depression have impaired mesolimbic DA signaling and self-administer excessive amounts of psychostimulants in an oral consumption paradigm compared to SwHi rats bred for high activity in the forced swim test (Weiss *et al.*, 1998, Weiss *et al.*, 2008, West *et al.*, 1999a, West *et al.*, 1999b). This constellation of phenotypes; a hypofunctional reward system characterized by depression-like behavior, combined with an increased propensity to self-administer psychostimulants, is consistent with the self-medication hypothesis and provides an intriguing model for studying depression and addiction comorbidity. However, oral drug self-administration paradigms have some inherent limitations, as they are subject to potential differences in taste and involve an inborn, "automatic" behavior (drinking) rather than a learned, operant behavior that is more reminiscent of human drug addiction. To confirm the persistence of DA system dysfunction in the depression-sensitive line, we first tested amphetamine-induced locomotion in more recent generations of SwLo and SwHi rats. Next, to further explore motivation for drug-seeking behavior, we assessed several aspects of operant i.v. amphetamine and cocaine self-administration in SwLo and SwHi rats.

2. Materials and methods

2.1. Animals

Male SwHi and SwLo rats were bred in-house, as described (Weiss *et al.*, 1998), and were 2–4 months of age at the time of testing. All subjects were singly housed and received *ad libitum* access to food and water unless otherwise noted. Rats were maintained in a temperature-controlled environment on a 12 h reverse light/dark cycle with the lights on from 1900 to 0700 hours for self-administration experiments. For the amphetamine locomotion experiments, rats were maintained on a conventional 12 h light/dark cycle with the lights on from 0700 to 1900 hours.

Rats used for the self-administration experiments were acclimated to the vivarium for 1 week prior to food training. All animals were treated in accordance with NIH policy, and experiments were approved by the Emory Institutional Animal Care and Use Committee.

2.2. Amphetamine-induced locomotor activity

Rats were individually housed in clear acrylic cages in an activity-monitor room with *ad libitum* access to food and water. Movement was tracked using eight parallel infrared beams positioned at 5-cm intervals along the length of the cage. To exclude repetitive movements in a small area, each beam break that was different from the previous four breaks was recorded by a computer as a unit of "ambulatory activity." Rats were allowed to habituate to the room for 3 days and were handled for several minutes each day. All animals received a vehicle injection (0.9% saline) and, 2 days later, an injection with amphetamine (0.5 or 1.0 mg/kg in a volume of 5 ml/kg; Sigma-Aldrich, St. Louis, MO). Ambulatory activity was measured for 1 h immediately following injection. Each animal was tested with a single dose of amphetamine.

2.3. Food training

Prior to catheterization surgery, rats were trained to lever-press on a fixed ratio-1 (FR1) schedule for food (45 mg pellets; Fisher Scientific, Pittsburgh, PA) in standard rat operant chambers (Med Associates, St Albans, VT) as we have described (Schroeder *et al.*, 2010). Each chamber was equipped with a house light, two retractable levers (active and inactive), stimulus lights above both levers, and a food pellet dispenser. Inactive lever presses had no consequence. A computer with MED-PC software (MED Associates) controlled the program and recorded data. Food training sessions lasted for 8 h, or until the animal obtained at least 100 food pellets with a 70% selection for the active lever. Most rats achieved these criteria in a single session, although some required a few sessions.

2.4. Surgery

Rats were anesthetized with isoflurane and implanted with intravenous jugular catheters using standard methods, as we have described (Schroeder *et al.*, 2010). Catheters were flushed twice daily with 0.05 ml gentamicin (4 mg/ml) and 0.1 ml heparin solution (30 U/ml in sterile saline) for three days following surgery, then once daily. Catheter patency was verified by infusing methohexital sodium (20 mg/ml, IV), which results in rapid muscle tone loss when administered intravenously. Rats were allowed at least 5 days of recovery time before commencing self-administration experiments.

2.5. Amphetamine self-administration

Daily self-administration sessions on a FR1 schedule lasted for a maximum of 2 h or until rats received 40 drug infusions. At the beginning of each session, rats received a non-contingent infusion of amphetamine (0.1 mg/kg, i.v.; Sigma-Aldrich). During the sessions, each active lever press resulted in an amphetamine infusion (0.1 mg/kg in a volume of 167 μl/kg) and illumination of a stimulus light above the lever. A timeout period of 20 s followed the infusion, in which active lever presses had no programmed consequences. After the timeout period, the stimulus light was extinguished. Inactive lever presses were recorded, but had no programmed consequences. Daily FR1 sessions continued until the rats met the criteria for stable responding (number of drug infusions varied by <20% of the mean, active lever response was at least 20, and preference for the active lever was at least 75% for 3 consecutive days, with a minimum of 5 total days of cocaine self-administration). The day after reaching maintenance criteria for FR1 responding at the 0.1 mg/kg/infusion dose, rats were trained on a FR1 schedule with 0.25 mg/kg amphetamine. After reaching criteria for the second FR1 paradigm, the progressive ratio (PR) schedule commenced, in

which each subsequent infusion of amphetamine (0.1 mg/kg) required a greater number of active lever presses than the last, as described (Richardson and Roberts, 1996). The equation used for the number of active presses for each infusion was:

Response Requirement (rounded to nearest integer) $= (5e^{(injection\ number*0.2)}) - 5$, such that the response requirements for the first 25 infusions were 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, and 737. Amphetamine infusions were accompanied by the same programmed consequences as described for the FR-1 schedule. Sessions lasted until the rats reached breakpoint, defined as the number of infusions received prior to a 1 h period in which no rewards were obtained, or for a maximum of 6 h. Rats were considered to have reached a stable response level using the same criteria as the FR1 schedule, but for a minimum of 3 total days on the PR schedule. A subset of the rats were then tested for PR responding for a higher dose of amphetamine (0.25 mg/kg/infusion).

2.8. Cocaine self-administration and reinstatement

Separate groups of rats were used for cocaine self-administration experiments, and conditions were identical to those used for amphetamine self-administration, except that the reinforcer for the FR1 and PR sessions was cocaine (0.5 mg/kg/infusion; National Institute of Drug Abuse Drug Supply Program, Bethesda, MD).

The day following meeting criteria for stable PR responding, lever pressing was extinguished in daily 2 h sessions that had the same contingencies as the FR1 schedule, except responding on the active lever had no programmed consequences and did not result in a cocaine infusion. Behavior was considered extinguished when active lever presses over 3 consecutive days were <25% of the average number of active lever presses during the last 3 days of progressive ratio.

The day following meeting extinction criteria, rats were pretreated with cocaine (10 mg/kg, i.p.) immediately before a 2 h session reinstatement session under extinction conditions. A subset of the rats were also tested for reinstatement following administration of a lower dose of cocaine (1 mg/kg, i.p.).

2.9. Food self-administration and reinstatement

Separate groups of rats were used in the food self-administration experiments, and FR1, PR, extinction, and reinstatement conditions were identical to those used for drug self-administration, with the following exceptions. Rats were placed on restricted diets of 16 g of normal rat chow per day, which was given at least 1 h after the end of food self-administration sessions. Active lever presses were reinforced with a 45 mg food pellet (Fisher Scientific), and sessions lasted for 1 h or when 60 pellets were obtained. Following extinction, rats were reinstated for food in a 2 h session as we have described previously (Schroeder *et al.*, 2010). At the beginning of the session, 3 food pellets were non-contingently delivered in the first 10 s, and a food pellet was delivered non-contingently every 3 min. Active lever responses had no programmed consequences during reinstatement.

2.10. Statistical analysis

Data were analyzed by Student’s t-test when comparing 2 groups, and by ANOVA followed by Bonferroni post hoc tests when comparing more than 2 groups, using Prism 5.0 for Macintosh.

3. Results

3.1. SwLo rats have decreased amphetamine-induced locomotion

We reported previously that amphetamine-induced locomotion is attenuated in SwLo rats compared to SwHi rats (West *et al.*, 1999a). Because those data were obtained more than a decade and dozens of generations ago, we determined whether that phenotype has continued to be co-inherited with the phenotype being selected for (low activity in the forced swim test). We found that amphetamine-induced locomotion was still reduced in recent generations of SwLo rats (Fig. 1). A two-way ANOVA showed a main effect of line ($F_{1,26}$=20, p<0.001), dose ($F_{2,26}$=23.07, p<0.0001), and a line x dose interaction ($F_{2,26}$=4.08, p<0.05). Posthoc tests revealed that amphetamine-induced locomotion was significantly lower in SwLo rats compared with SwHi rats at both the 0.5 mg/kg (t=3.937, p<0.01) and 1 mg/kg (t=2.57, p<0.05) doses. These results indicate that a dysfunctional DA system has persisted in SwLo rats.

3.2. Amphetamine- and cocaine-seeking behavior during progressive ratio and reinstatement responding is attenuated in SwLo rats

To determine whether the differences between SwLo and SwHi rats in stimulant-induced locomotion and oral consumption extended to operant drug-seeking behavior, we assessed several aspects of i.v. amphetamine and cocaine self-administration. While no differences were detected during FR1 responding for amphetamine at two different doses (0.1 and 0.25 mg/kg/infusion), SwLo rats had a significantly lower breakpoint during PR self-administration of both doses compared to SwHi rats (Fig. 2). A two-way ANOVA showed a main effect of line ($F_{1,11}$=16.64, p<0.01), and posthoc tests revealed that breakpoint was significantly lower in SwLo rats at the 0.1 mg/kg (t=3.21, p<0.05) and the 0.25 mg/kg (t=2.67, p<0.05) doses. Inactive lever presses were low during all phases and were not significantly different between lines.

Results were similar for cocaine-self administration (Fig. 3). No differences were detected during FR1 responding for cocaine, but SwLo rats had a significantly lower breakpoint during PR self-administration (t=2.37, p<0.05). While the low priming dose of cocaine (1 mg/kg, i.p.) did not induce reinstatement behavior in rats of either line, the high priming dose of cocaine (10 mg/kg, i.p.) significantly reinstated active lever pressing compared to extinction responding in SwHi rats, but not SwLo rats. A two-way ANOVA showed a main effect of self-administration phase ($F_{2,30}$=20.77, p<0.0001) and line ($F_{1,30}$=5.16, p<0.0001), and a phase x line interaction was just at the significance cutoff ($F_{2,30}$=3.31, p=0.05). Posthoc analysis revealed that active lever responding at the high dose was significantly higher in SwHi rats compared to extinction (t=5.25, p<0.001) and compared to SwLo rats (t=3.41, p<0.05). Inactive lever presses were low during all phases and were not significantly different between lines.

3.3. Food-primed reinstatement of food seeking is reduced in SwLo rats

To determine whether the differences in amphetamine and cocaine responding between SwLo and SwHi rats were specific to stimulant drugs or generalized to natural rewards, we assessed several aspects of operant food self-administration (Fig. 4). No significant differences were observed between lines during FR1 or PR food self-administration tested, but food-primed reinstatement responding was reduced in SwLo rats. A two-way ANOVA showed a main effect of phase ($F_{1,14}$=6.15, p < 0.05) and line ($F_{1,14}$=6.61, p<0.05). Posthoc analysis revealed that active lever presses were significantly lower in SwLo rats compared with SwHi rats during reinstatement (t=2.53, p<0.05). Active lever presses also tended to be lower in SwLo rats during extinction, but the difference did not reach statistical significance.

Inactive lever presses were low during all phases and were not significantly different between lines.

4. Discussion

4.1. SwLo rats as a model of depression and addiction comorbidity

As summarized in the Introduction, depression and drug addiction are comorbid disorders, potentially due to an attempt by depressed individuals to compensate for intrinsic anhedonia and motivational deficiencies by taking drugs (i.e. the "self-medication" hypothesis). Because animal models have been particularly useful for understanding the neurobiological substrates underlying depression and addiction individually, an animal model displaying features of both disorders might be equally informative for unraveling the underpinnings of comorbidity. We examined operant psychostimulant self-administration in SwLo and SwHi rats for 3 reasons. First, SwLo animals have low activity in the forced swim test (the trait they were selected for) and other anhedonic-like behaviors (Weiss *et al.*, 1998) (our unpublished data). Second, they display decreased amphetamine-induced locomotor activity, altered behavioral responses to apomorphine, and impaired DA signaling in the nucleus accumbens (West *et al.*, 1999a, West *et al.*, 1999b). Third, SwLo rats voluntarily consume more cocaine and amphetamine in oral self-administration paradigms (Weiss *et al.*, 2008). This constellation of phenotypes; a hypofunctional reward system characterized by depression-like behavior and anhedonia, combined with an increased propensity to self-administer psychostimulants, is consistent with the self-medication hypothesis and provides an intriguing model to study depression and addiction comorbidity. The SwLo rats are also appealing because their behavioral phenotypes are heritable, and both depression and addiction have substantial genetic components in humans (Levinson, 2006, Nestler, 2000). While we did not test non-selected "wild-type" rats in this study, our previous results have shown that the relevant phenotypes of non-selected rats (e.g., forced swim test activity, oral amphetamine consumption) typically fall somewhere in between those of SwLo and SwHi rats (Weiss *et al.*, 1998, Weiss *et al.*, 2008).

4.2. Operant psychostimulant self-administration

Contrary to our predictions and previous oral consumption results, SwLo rats actually displayed decreased amphetamine- and cocaine-seeking behavior compared with SwHi rats. These differences were particularly evident when contingencies were high (PR schedule) or non-reinforced (reinstatement). These results suggest that the self-medication hypothesis may not be applicable to the SwLo rats. These animals have hypofunctional DA systems, which may suppress multiple stimulant-induced behaviors, including locomotor activity and operant self-administration. The differences between SwHi and SwLo rats were particularly evident during drug-primed reinstatement, a behavior known to require DA transmission in the NAc (Schmidt *et al.*, 2005). Thus, it is possible that hypofunctional accumbal DA system in the SwLo rats can account for the decrease in drug-seeking behavior observed in these animals. Interestingly, the levels of DA and its metabolites in the striatum of SwLo rats are similar to that of SwHi rats, but are low in the prefrontal cortex, while postsynaptic DA receptor signaling is altered in SwLo rats (Weiss *et al.*, 2008, West *et al.*, 1999b). We did not measure DA release or transmission in this study, and it is possible that other neurotransmitter systems that are impacted by psychostimulants, such as norepinephrine, are altered in SwLo rats and contribute to the phenotypes.

A trivial explanation for the increased oral drug intake observed in the SwLo rats could be altered taste preferences. However, this seems unlikely because SwLo rats consumed more amphetamine solution regardless of whether sucrose was added to it or not (Weiss *et al.*, 2008). Thus, we offer several alternative explanations for the discrepancy between oral and

operant psychostimulant-seeking behavior. Because operant behaviors require learning, while drinking is innate, differences in cognitive performance could contribute to differences in operant behavior. However, SwLo and SwHi rats acquired self-administration at similar rates and learn spatial memory tasks with equal efficiency (our unpublished data). The explanation we currently favor is that the low exploratory and drug-induced motor activity may be masking an increased propensity for psychostimulant intake. Compared to SwHi rats, SwLo animals have reduced activity under circumstances that tend to elicit active, assertive motor behavior, such as a novel environment (Weiss *et al.*, 1998), which could affect motivation to execute operant drug-seeking responses. In addition, amphetamine-induced locomotor activity, which could help drive operant responding for the drug during the self-administration sessions, is also impaired in SwLo rats. Consistent with this idea, individual and selected differences in self-administration are often (although not always) positively correlated with novelty-seeking and stimulant-induced locomotor activity (Belin *et al.*, 2011, Mandt *et al.*, 2008, Meyer *et al.*, 2010, Schramm-Sapyta *et al.*, 2011). Food-primed reinstatement of food seeking is also impaired in SwLo rats, consistent with a decreased motivation to perform operant tasks. Although we tested 2 different doses of amphetamine and 1 dose of cocaine, it is important to note that we did not examine full dose-response relationships in this study. Thus, it is possible that different results would be obtained if additional doses were tested.

4.3. Conclusion

We undertook this study to determine whether the increase in oral psychostimulant self-administration observed in a rodent model of depression with impaired DA transmission extended to operant self-administration. Contrary to our hypothesis and the oral self-administration data, SwLo rats displayed reduced drug-seeking behavior during PR and reinstatement responding for both cocaine and amphetamine. Thus, at the doses tested, these results do not support the use of SwLo rats to study the self-medication hypothesis of drug addiction, and highlight the different outcomes that can be obtained using oral vs. operant self-administration paradigms. Future studies examining these rats in other addiction-related paradigms that measure drug seeking but do not require operant responses, such as conditioned place preference, are warranted. It may also be informative to test the self-administration behavior of SwHi and SwLo rats using additional cocaine and amphetamine doses, as well as other classes of drugs such as opiates and nicotine.

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Highlights

- We tested psychostimulant responses in a rat model of depression (SwLo rats)
- Amphetamine-induced locomotion is attenuated in SwLo rats
- SwLo rats have a lower breakpoint on a PR schedule of self-administration
- Drug-primed reinstatement is reduced in SwLo rats

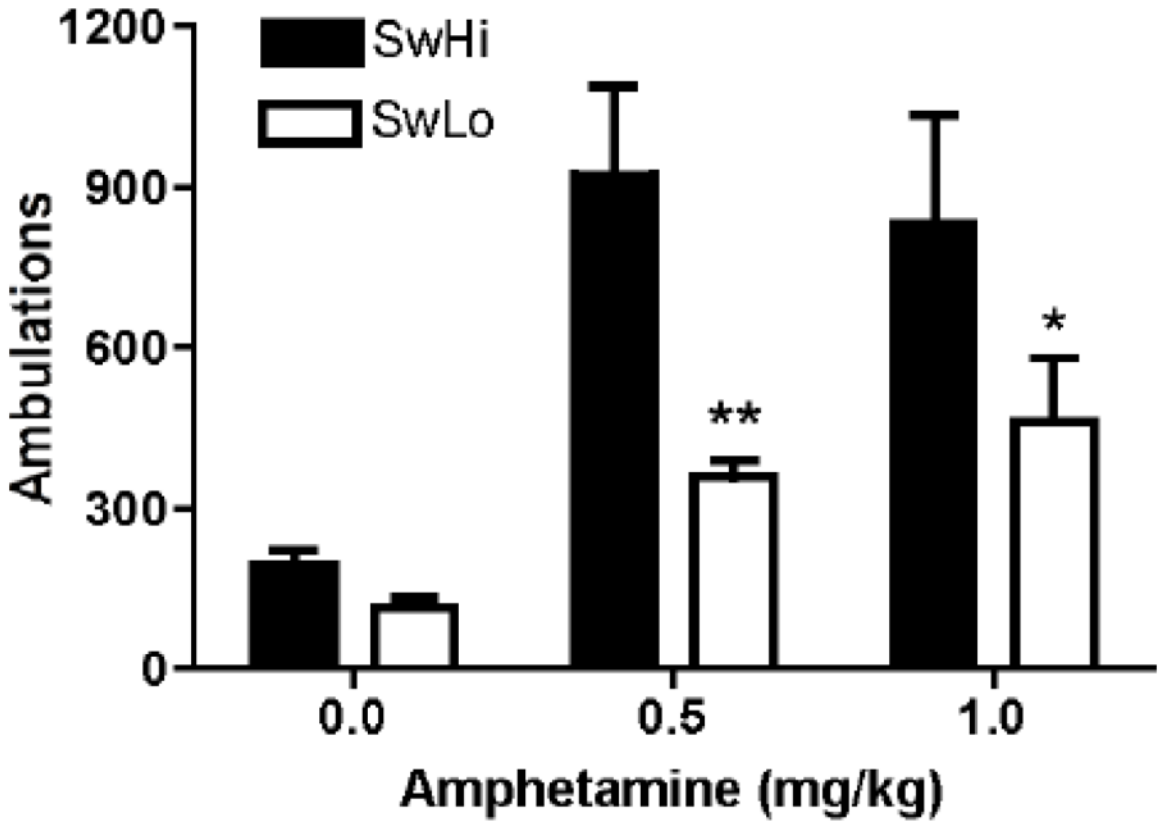

Fig. 1. Amphetamine-induced locomotion is reduced in SwLo rats

SwHi and SwLo rats were injected with vehicle (n=8 per group) or amphetamine (0.5 or 1 mg/kg, i.p.; n=4 per group), and locomotor activity was measured for 1 h. Shown are mean ± SEM ambulations (consecutive beam breaks). *p<0.05, **p<0.01 compared with SwHi rats at that dose.

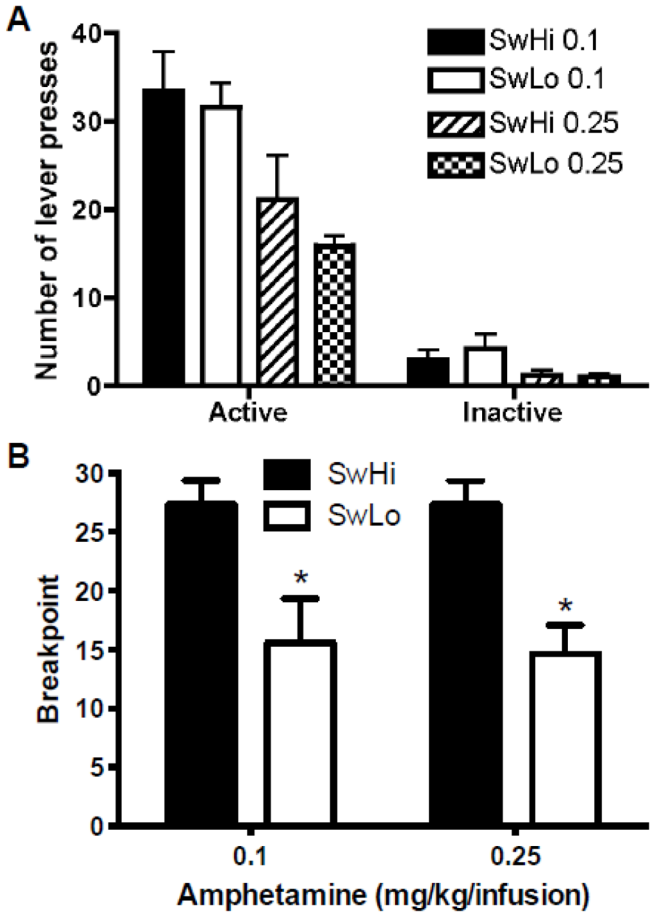

Fig. 2. Amphetamine self-administration in SwHi and SwLo rats

SwHi and SwLo rats were trained to self-administer amphetamine (0.1 mg/kg/infusion) on an FR1 schedule. After reaching maintenance criteria, rats were trained to self-administer a higher dose of amphetamine (0.25 mg/kg/infusion) on an FR1 schedule. After reaching maintenance criteria for the higher dose, rats were tested for PR responding for the lower dose (0.1 mg/kg). Shown is the mean ± SEM of (A) active and inactive lever presses during stable FR1 responding at 0.1 mg/kg/infusion (SwHi, n=7; SwLo, n=5) and 0.25 mg/kg/infusion (SwHi, n=5; SwLo, n=5) and (B) number of rewards earned at breakpoint during stable PR responding at 0.1 mg/kg/infusion (SwHi, n=5; SwLo, n=4) and 0.25 mg/kg/infusion (SwHi, n=2; SwLo, n=4). *$p<0.05$ compared to SwHi rats.

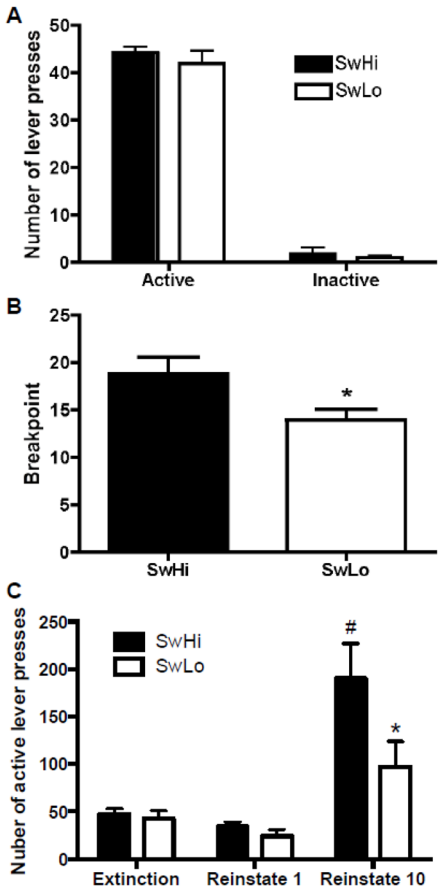

Fig. 3. Cocaine self-administration and reinstatement in SwHi and SwLo rats

Rats were trained to self-administer cocaine (0.5 mg/kg/infusion) on an FR1 schedule. After reaching maintenance criteria, rats were tested for PR responding at the same dose of cocaine. Rats were then extinguished and tested for cocaine-primed (1 or 10 mg/kg i.p.) reinstatement ("Reinstate 1" and "Reinstate 10", respectively) the day after meeting extinction criteria. Shown is mean ± SEM of (A) active and inactive lever presses during stable FR1 responding (SwHi, n=7; SwLo, n=8), (B) number of rewards earned at breakpoint during stable PR responding (SwHi, n=7; SwLo, n=8), and (C) active lever presses during stable extinction and reinstatement (n=6 per group). *$p<0.05$ compared to reinstatement for SwHi rats, #$p<0.001$ compared to extinction for SwHi rats.

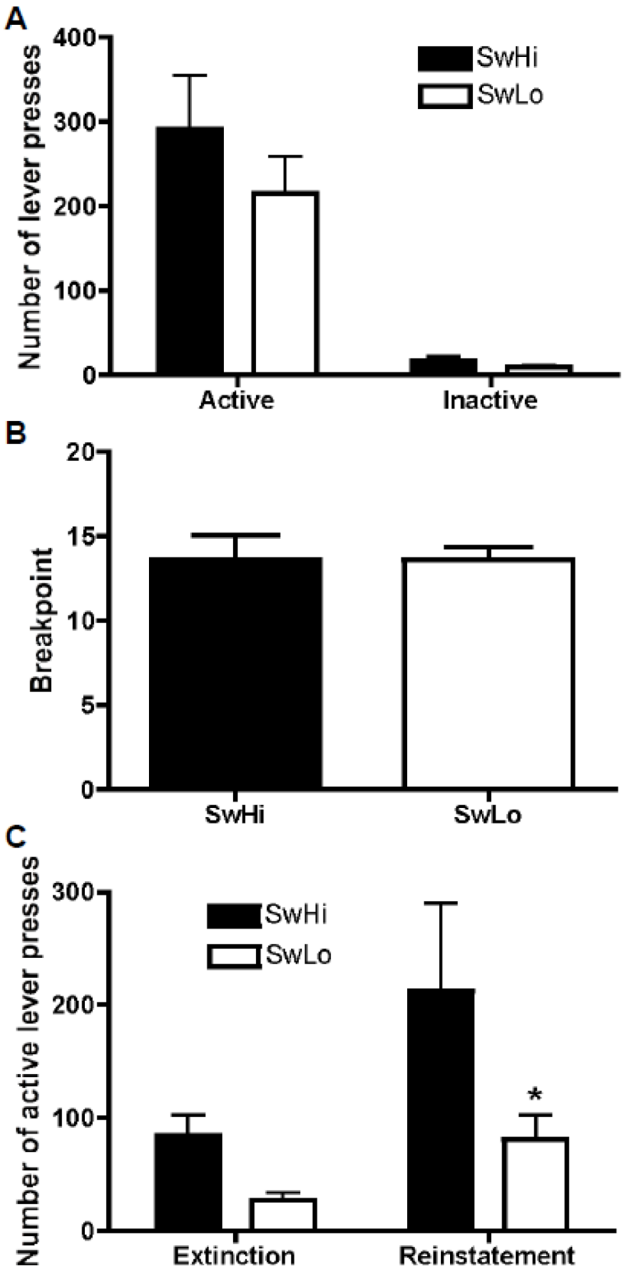

Fig. 4. Food self-administration and reinstatement in SwHi and SwLo rats

Rats were trained to self-administer 45 mg food pellets on an FR1 schedule. After reaching maintenance criteria, rats were tested for PR responding for food pellets. Rats were then extinguished and tested for food-primed reinstatement the day after meeting extinction criteria. Shown is mean ± SEM of (A) active and inactive lever presses during stable FR1 responding, (B) number of rewards earned at breakpoint during stable PR responding, and (C) active lever presses during stable extinction and reinstatement. *$p<0.05$ compared to reinstatement for SwHi rats. N=4–5 per group.