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Contextual and behavioral control of antipsychotic sensitization induced by haloperidol and olanzapine

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Abstract

Repeated administration of haloperidol (HAL) and olanzapine (OLZ) causes a progressively enhanced disruption of the conditioned avoidance response (CAR) and a progressively enhanced inhibition of phencyclidine (PCP)-induced hyperlocomotion in rats (termed antipsychotic sensitization). Both actions are thought to reflect intrinsic antipsychotic activity. The present study examined the extent to which antipsychotic-induced sensitization in one model (e.g. CAR) can be transferred or maintained in another (e.g. PCP hyperlocomotion) as a means of investigating the contextual and behavioral controls of antipsychotic sensitization. Well-trained male Sprague-Dawley rats were first repeatedly tested in the CAR or the PCP (3.2 mg/kg, subcutaneously) hyperlocomotion model under HAL or OLZ for 5 consecutive days. Then they were switched to the other model and tested for the expression of sensitization. Finally, all rats were switched back to the original model and retested for the expression of sensitization. Repeated HAL or OLZ treatment progressively disrupted avoidance responding and decreased PCP-induced hyperlocomotion, indicating a robust sensitization. When tested in a different model, rats previously treated with HAL or OLZ did not show a stronger inhibition of CAR-induced or PCP-induced hyperlocomotion than those treated with these drugs for the first time; however, they did show such an effect when tested in the original model in which they received repeated antipsychotic treatment. These findings suggest that the expression of antipsychotic sensitization is strongly influenced by the testing environment and/or selected behavioral response under certain experimental conditions. Distinct contextual cues and behavioral responses may develop an association with unconditional drug effects through a Pavlovian conditioning process. They may also serve as occasion setters to modulate the expression of sensitized responses. As antipsychotic sensitization mimics the clinical effects of antipsychotic treatment, understanding the neurobiological mechanisms of antipsychotic sensitization and its contextual control would greatly enhance our understanding of the psychological and neurochemical nature of antipsychotic treatment in the clinic.

Keywords: behavioral sensitization, conditioned avoidance response, haloperidol, olanzapine, phencyclidine, rat, time course of antipsychotic effect

Introduction

The conditioned avoidance response (CAR) and phencyclidine (PCP)-induced hyperlocomotion are two widely used animal models for the study of antipsychotic drugs. Both models have high predictive validity for antipsychotic efficacy, as all clinically approved antipsychotics [e.g. haloperidol (HAL), olanzapine (OLZ), and risperidone], but not other classes of psychotherapeutic drugs (e.g. anxiolytics, antidepressants), selectively disrupt avoidance responding, and inhibit the PCP-induced increase in motor activity upon acute administration (Gleason and Shannon, 1997; Li *et al.*, 2004b). More importantly, both models are capable of capturing the time course of antipsychotic treatment in the clinic. With repeated drug administration, antipsychotics progressively enhance their disruption of avoidance responding (Li *et al.*, 2009a, 2009b, 2010; Mead and Li, 2010) and their inhibition of PCP-induced hyperlocomotion over the drug treatment period (Sun *et al.*, 2009). This progressive increase in an-

tipsychotic effects due to repeated drug administration is termed as antipsychotic sensitization. This behavioral pattern is consistent with clinical observations showing that antipsychotic action increases in magnitude with repeated treatment over time (Agid *et al.*, 2003, 2006; Kapur *et al.*, 2005; Leucht *et al.*, 2005; Emsley *et al.*, 2006; Glick *et al.*, 2006; Raedler *et al.*, 2007).

In comparison with extensive research on behavioral sensitization induced by psychotomimetic drugs (e.g. amphetamine, cocaine, PCP, etc.; Robinson and Becker, 1986; Pierce and Kalivas, 1997), antipsychotic sensitization, especially the type induced by atypical antipsychotics (e.g. OLZ, clozapine, risperidone) is relatively new and less well understood. This situation is peculiar, given the fact that antipsychotics, such as drugs of abuse, are often taken repeatedly by people for a prolonged period of time, and antipsychotic sensitization is thought to be an important mechanism supporting the maintenance of the antipsychotic effect (Li *et al.*, 2007). Thus, antipsychotic sensitization should have received more attention than it

currently has. One major issue that may have contributed to this lack of attention is the difficulty in demonstrating its existence. For example, in studies using the prepulse inhibition paradigm, behavioral sensitization has never been consistently established among different antipsychotics (Geyer *et al.*, 2001; Li *et al.*, 2011a).

As repeated antipsychotic treatment induces sensitization in both the CAR and the PCP hyperlocomotion models, and both sensitizations putatively reflect the same antipsychotic activity over time, one interesting and critically important question is whether antipsychotic-induced sensitization is situation specific. In other words, could the antipsychotic-induced sensitization in one model (e.g. CAR) be transferred or maintained in another model (e.g. PCP hyperlocomotion)? We postulated that studying across-model transfer of antipsychotic sensitization would allow us to investigate the contextual and behavioral controls of antipsychotic sensitization. If antipsychotic sensitization results from inevitable neurobiological adaptations produced by the direct pharmacological actions of the drug (Tarsy and Baldessarini, 1974), it should be transferrable across models and suggests that contextual and behavioral variables have little influence on the development of antipsychotic sensitization. In contrast, if the context and the behaviors associated with drug administration have a powerful control on the expression of antipsychotic sensitization, it should not be transferrable between models.

The present study addressed this question. We tested HAL and OLZ, two representative drugs for typical and atypical antipsychotics, and examined bidirectional transfer between the CAR and the PCP models. Our general approach was to induce behavioral sensitization in one model through repeated drug administration, then to test its expression in another model, and finally to retest its expression back in the first model. Our results showed that HAL and OLZ sensitization in both models only manifested itself when the induction condition was the same as the test condition. These results are in general agreement with research on psychomotor sensitization, which also shows that the expression of behavioral sensitization is greatly impacted by contextual cues (Vezina and Stewart, 1984; Anagnostaras and Robinson, 1996; Robinson *et al.*, 1998) and selected behavior responses (Ohmori *et al.*, 2000).

Methods

Subjects

Adult male Sprague-Dawley rats (226–250 g upon arrival, Charles River, Portage, Michigan, USA) were used. They were housed two per cage in 48.3 × 26.7 × 20.3-cm transparent polycarbonate cages under 12-h light/dark conditions (light on between 6:30 a.m. and 6:30 p.m.). Room temperature was maintained at 22 ± 1°C with a relative humidity of 45–60%. Food and water were freely avail-

able. Subjects were allowed at least 1 week of habituation to the animal facility before being used in experiments. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska-Lincoln.

Drugs and choice of doses

The injection solution of HAL (5.0 mg/ml ampoules; Shanghai Xudong Haipu Pharmaceutical Co., Ltd, Shanghai, China) was obtained by mixing the stock with sterile water. OLZ (a gift from the National Institute of Mental Health Drug Supply Program) was dissolved in 1.0% glacial acetic acid in distilled water. PCP hydrochloride (a gift from the National Institute of Drug Administration Chemical Synthesis and Drug Supply Program) was dissolved in 0.9% saline. All drugs were administered subcutaneously. In the first two experiments (from CAR to PCP), we tested three doses of HAL (0.03, 0.05, and 0.10 mg/kg) and OLZ (0.5, 1.0, and 2.0 mg/kg). At these doses, HAL and OLZ produced a comparable level of disruption on avoidance responding, which is considered a validated behavioral index of antipsychotic action (Li *et al.*, 2004a, 2007, 2009a, 2009b; Mead and Li, 2010). Furthermore, both drugs at these doses give rise to 50–80% striatal dopamine D₂ occupancy in rats, which is comparable with values observed in schizophrenic patients (Kapur *et al.*, 2005). On the basis of the findings from the first two experiments and our published work (Sun *et al.*, 2009), we tested HAL at 0.05 mg/kg and OLZ at 1.0 mg/kg in the last two experiments (from PCP to CAR) because they induce a robust sensitization effect in the PCP hyperlocomotion model (Sun *et al.*, 2009).

Two-way avoidance conditioning apparatus

Eight identical two-way shuttle boxes custom designed and manufactured by Med Associates (St. Albans, Vermont, USA) were used. Each box was housed in a ventilated, sound-insulated isolation cubicle (96.52-cm width × 35.56-cm diameter × 63.5-cm height). Each box was 64-cm long, 30-cm high (from grid floor), and 24-cm wide, and was divided into two equal-sized compartments by a partition with an arch-style doorway (15-cm high × 9-cm wide at base). A barrier (4-cm high) was placed between the two compartments, so the rats had to jump from one compartment to the other. The grid floor consisted of 40 stainless-steel rods with a diameter of 0.48 cm, spaced 1.6 cm apart center to center, through which a scrambled foot shock [unconditioned stimulus (US), 0.8 mA, maximum duration: 5 s] was delivered by a constant current shock generator (Model ENV-410B) and scrambler (Model ENV-412). The rat's location and crossings between compartments were monitored by a set of 16 photobeams (ENV-256-8P) affixed at the bottom of the box (3.5 cm above the grid floor). Illumination was provided by two house lights mounted at the top of each compartment. The conditioned stimulus (CS; i.e., 76 dB white noise) was produced by a speaker (ENV 224 AMX)

mounted on the ceiling of the cubicle, centered above the shuttle box. Background noise (approximately 74 dB) was provided by a ventilation fan affixed at the top corner of each isolation cubicle. All training and testing procedures were controlled by Med Associates programs running on a computer.

Motor activity monitoring apparatus

Sixteen activity boxes were housed in a quiet room. The boxes were 48.3 × 26.7 × 20.3-cm transparent polycarbonate cages, which were similar to the home cages, but were each equipped with a row of six photocell beams (7.8 cm between adjacent beams) placed 3.2 cm above the floor of the cage. A computer detected the disruption of the photocell beams and recorded the number of beam breaks. All experiments were run during the light cycle.

Experiment 1: Transferability of haloperidol-induced sensitization from the conditioned avoidance response model to the phencyclidine hyperlocomotion model

This experiment examined whether the sensitization effect induced by repeated HAL treatment in the CAR model was transferrable to the PCP-induced hyperlocomotion model. The experiment comprised the following three phases: avoidance training/sensitization induction in the CAR, sensitization assessment in the PCP hyperlocomotion model, and sensitization reassessment in the CAR model.

Avoidance training/sensitization induction in the conditioned avoidance response: Seventy-two rats (run in two batches) were first habituated to the CAR boxes for 2 days (20 min/day). Then, they were trained for conditioned avoidance responding for 10 sessions over a 2-week period. Each session consisted of 30 trials. Every trial started by presenting a white noise (CS) for 10 s, followed by a continuous scrambled foot shock [0.8 mA, US, maximum duration = 5 s] on the grid floor. If a rat moved from one compartment into the other within the 10 s of CS presentation, it avoided the shock and this shuttling response was recorded as avoidance. If the rat remained in the same compartment for more than 10 s and made a crossing upon receiving the foot shock, this response was recorded as escape. If the rat did not respond during the entire 5-s presentation of the shock, the trial was terminated and escape failure was recorded. The total number of avoidance responses was recorded for each session. Intertrial intervals varied randomly between 30 and 60 s.

At the end of the training session, 59 rats reached the training criterion (> 70% avoidance in each of the last two sessions). They were first matched on avoidance performance on the last training day (i.e., predrug) to create blocks of rats ($n = 3\text{--}4$ rats/block) that were approximately equal in performance. Within each block, they were then randomly assigned to one of four groups: HAL, 0.03 mg/kg (HAL 0.03, $n = 7$); HAL, 0.05 mg/kg (HAL 0.05, $n = 7$); HAL, 0.10 mg/kg (HAL 0.10, $n = 7$); and

vehicle (VEH, $n = 38$), and tested daily under the CS-only (no shock, 30 trials/daily sessions) condition for 5 consecutive days. The CS-only condition was used to control the possible confound of the number of shocks received and to exclude any possible relearning effect caused by the presence of the US. During each drug test, rats were first injected with HAL or sterile water. One hour later, they were placed in the CAR boxes and tested. Because of an error in data collection, data for seven rats were lost (five VEH rats, one HAL 0.05, and one HAL 0.10). Thus, the final numbers of rats entered into the subsequent drug testing were as follows: HAL 0.03 ($n = 7$), HAL 0.05 ($n = 6$), HAL 0.10 ($n = 6$), and VEH ($n = 33$).

Sensitization assessment in the phencyclidine hyperlocomotion model: One day after the CAR drug testing, rats were habituated to the motor activity testing boxes for 30 min. On day 2, rats that were previously treated with HAL in the CAR received the same HAL treatment, followed by PCP (termed HAL-HAL 0.03 + PCP, HAL-HAL 0.05 + PCP, and HAL-HAL 0.10 + PCP groups). Rats that were previously treated with sterile water in the CAR were randomly assigned to five groups: three groups received HAL, followed by PCP (termed VEH-HAL 0.03 + PCP, $n = 5$; VEH-HAL 0.05 + PCP, $n = 6$; and VEH-HAL 0.10 + PCP, $n = 5$), and two groups received sterile water, followed by PCP or saline (termed VEH-VEH + PCP, $n = 8$ and VEH-VEH + VEH, $n = 9$). During this test, rats were first injected with HAL or sterile water. Immediately after injection, they were placed in the motor activity testing boxes for 30 min. At the end of the 30-min period, rats were taken out and injected with either VEH (0.9% saline) or PCP (1.6 mg/kg, subcutaneously) and placed back in the boxes for another 60 min (Sun *et al.*, 2009). Motor activity (number of photobeam breaks) was measured at 5-min intervals throughout the entire 90-min testing session.

Sensitization reassessment in the conditioned avoidance response: One day after the PCP hyperlocomotion test, all rats were returned back to the CAR task and tested drug-free for one session under the CS-only (no shock) condition and retrained for one session under the CS-US condition to bring their avoidance back to the predrug level. A final challenge test for sensitization was conducted 24 h after the retraining session, during which all rats were injected with HAL 0.03 and tested for avoidance performance in the CS-only condition (30 trials) 1 h later. Table 1 presents the group information in different phases of Experiment 1.

Experiment 2: Transferability of olanzapine-induced sensitization from the conditioned avoidance response model to the phencyclidine hyperlocomotion model

This experiment examined whether the sensitization induced by repeated OLZ treatment in the CAR model was transferrable to the PCP hyperlocomotion model. The basic procedure was identical to that of Experiment 1, with the exception that HAL (0.03, 0.05, and 1.0 mg/kg) was

Table 1. A schematic depiction of the experimental groups formed at different phases of Experiment 1.

CAR 4 groups	Locomotor activity 8 groups	CAR 4 groups
VEH (<i>n</i> =33)	VEH-VEH + VEH (<i>n</i> =9)	VEH-HAL 0.03
	VEH-VEH + PCP (<i>n</i> =8)	
	VEH-HAL 0.03 + PCP (<i>n</i> =5)	
	VEH-HAL 0.05 + PCP (<i>n</i> =6)	
HAL 0.03 (<i>n</i> =7)	VEH-HAL 0.10 + PCP (<i>n</i> =5)	
HAL 0.05 (<i>n</i> =6)	HAL 0.03-HAL 0.03 + PCP	HAL 0.03-HAL 0.03
HAL 0.10 (<i>n</i> =6)	HAL 0.05-HAL 0.05 + PCP	HAL 0.05-HAL 0.03
	HAL 0.10-HAL 0.10 + PCP	HAL 0.10-HAL 0.03

Letters in **bold** indicate the type of treatments administered at different phases. CAR, conditioned avoidance response; HAL, haloperidol; PCP, phencyclidine; VEH, vehicle.

Table 2. A schematic depiction of the experimental groups formed at different phases of Experiment 2.

CAR 4 groups	Locomotor activity 8 groups	CAR 4 groups
VEH (<i>n</i> =35)	VEH-VEH + VEH (<i>n</i> =8)	VEH-OLZ 0.5
	VEH-VEH + PCP (<i>n</i> =7)	
	VEH-OLZ 0.5 + PCP (<i>n</i> =7)	
	VEH-OLZ 1.0 + PCP (<i>n</i> =6)	
OLZ 0.5 (<i>n</i> =7)	VEH-OLZ 2.0 + PCP (<i>n</i> =7)	
OLZ 1.0 (<i>n</i> =5)	OLZ 0.5-OLZ 0.5 + PCP	OLZ 0.5-OLZ 0.5
OLZ 2.0 (<i>n</i> =6)	OLZ 1.0-OLZ 1.0 + PCP	OLZ 1.0-OLZ 0.5
	OLZ 2.0-OLZ 2.0 + PCP	OLZ 2.0-OLZ 0.5

Letters in **bold** indicate the type of treatments administered at different phases. CAR, conditioned avoidance response; OLZ, olanzapine; PCP, phencyclidine; VEH, vehicle.

replaced by OLZ (0.5, 1.0, and 2.0 mg/kg). Seventy-two rats (run in two batches) were used, of which 58 reached the learning criterion. They were then randomly assigned to one of the following four groups in the initial CAR test phase: OLZ 0.5 mg/kg (OLZ 0.5, *n* = 7), OLZ 1.0 mg/kg (OLZ 1.0, *n* = 7), OLZ 2.0 mg/kg (OLZ 2.0, *n* = 7), and VEH (*n* = 37). At the end of the CAR testing phase, data for five rats were lost (two VEH rats, two OLZ 1.0, and one OLZ 2.0). Thus, the final numbers for each group entered in the subsequent drug testing were: OLZ 0.5: *n* = 7; OLZ 1.0: *n* = 5; OLZ 2.0: *n* = 6; and VEH: *n* = 35. In the PCP hyperlocomotion test phase, the VEH groups were split into five groups: VEH-OLZ 0.5 + PCP (*n* = 7), VEH-OLZ 1.0 + PCP (*n* = 6), VEH-OLZ 2.0 + PCP (*n* = 7), VEH-VEH + PCP (*n* = 7), and VEH-VEH + VEH (*n* = 8). In the final sensitization reassessment test, all of the rats were injected with OLZ 0.5. Table 2 depicts the group information in different phases of Experiment 2.

Experiment 3: Transferability of haloperidol-induced sensitization from the phencyclidine hyperlocomotion model to the conditioned avoidance response model

This experiment was a mirror experiment to Experiment 1 in the sense that it examined the opposite direction of sensitization transfer. We examined whether the sensitization-like effect induced by repeated HAL (0.05 mg/kg, subcutaneously) treatment in the PCP hyperlocomotion

model is transferrable to the CAR model. HAL 0.05 was tested because this dose produces a reliable sensitization effect (see Experiment 1 and Li *et al.*, 2010). The entire experiment comprised the following three phases: sensitization induction in the PCP hyperlocomotion model, sensitization assessment in the CAR, and sensitization reassessment in the PCP hyperlocomotion model.

Sensitization induction in the phencyclidine hyperlocomotion model. Thirty-two rats were first handled and habituated to the avoidance conditioning apparatus for 2 days (30 min/day) and then trained for 10 consecutive days to acquire robust conditioned avoidance responding. At the end of the training phase, 25 rats that had reached the training criterion were used in the subsequent tests. They were randomly assigned to the following two groups: HAL 0.05 (*n* = 8) and VEH (*n* = 17) groups. On day 1, rats were habituated in the motor activity boxes for 30 min. On day 2, rats were first injected with HAL (0.05 mg/kg) or VEH (sterile water) and then immediately placed in the boxes for 30 min. At the end of the 30-min period, they were taken out and injected with PCP (3.2 mg/kg) and placed back in the boxes for another 60 min. This procedure was repeated for another 4 days (a total of 5 testing days). Our previous work shows that repeated antipsychotic treatment (e.g. HAL, clozapine, OLZ, etc.) produces a robust sensitization effect in this PCP model (Sun *et al.*, 2009).

Sensitization assessment in the conditioned avoidance response: One day after the last (fifth) PCP hyperlocomotion test, all rats were given a CAR retraining session to bring their avoidance back to the predrug level. One day later, the sensitization assessment test was conducted. During this test, rats in the VEH group were randomly assigned to two subgroups: VEH-VEH (*n* = 9) and VEH-HAL 0.03 (*n* = 8) and received an injection of sterile water or HAL 0.03, respectively. Rats in the HAL 0.05 group were injected with HAL 0.03 (termed HAL 0.05-HAL 0.03 group). They were then tested for avoidance performance under the CS-only condition (no shock) for 30 trials 1 h after injection.

Sensitization reassessment in the phencyclidine hyperlocomotion model. One day after the sensitization test in the CAR, a final sensitization reassessment test was conducted back in the PCP locomotor model. All rats were first injected with HAL 0.03 and then immediately placed in the motor activity boxes for 30 min. At the end of the 30-min period, rats were taken out and injected with PCP (3.2 mg/kg) and placed back in the boxes for another 60 min. Motor activity was measured at 5-min intervals throughout the entire 90-min testing session.

Experiment 4: Transferability of olanzapine-induced sensitization from the phencyclidine hyperlocomotion model to the conditioned avoidance response model

This experiment was a mirror experiment to Experiment 2. It followed the same procedure as Experiment 3, with the

exception that HAL (0.05 mg/kg) was replaced by OLZ (1.0 mg/kg). Thirty-two rats were used, of which 26 rats reached the training criterion. They were then randomly assigned to OLZ 1.0 ($n = 9$) and VEH ($n = 17$) and tested in the PCP hyperlocomotion model for 5 days. During the CAR test phase, the VEH group was randomly split into two groups: VEH-VEH ($n = 8$) and VEH-OLZ 0.5 ($n = 9$), and received an injection of sterile water or OLZ 0.5, respectively. Rats in the OLZ 1.0 group received OLZ 0.5. In the sensitization reassessment test, all rats were administered OLZ 0.5, followed by PCP 3.2 30 min later.

Statistical analysis

All data were expressed as mean $\pm$ standard error of the mean. Data from the five drug testing sessions (e.g., avoidance response and PCP-induced motor activity) were analyzed using a factorial repeated-measures analysis of variance (ANOVA), with the between-subjects factor being drug group and the within-subjects factor being test session. One-way ANOVAs, followed by post-hoc Tukey honestly significant difference tests (for > 3 groups) were used to identify group differences on a specific testing session. For a two-group comparison, independent-samples t -tests were used. A conventional two-tailed level of significance at the 5% level was required.

Results

Experiment 1: Transferability of haloperidol-induced sensitization from the conditioned avoidance response model to the phencyclidine hyperlocomotion model *Repeated haloperidol treatment produced a progressively enhanced disruption of avoidance responding in a dose-dependent manner*

Figure 1a shows the number of avoidance responses made by the rats in the four groups during the five drug sessions. The three HAL groups showed a progressive across-session decrease in avoidance responding. The VEH group maintained a high level of avoidance responding throughout this phase. Repeated-measures ANOVA revealed a significant main effect of group [$F(3, 48) = 49.20$, $P < 0.001$] and session [$F(4, 192) = 11.64$, $P < 0.001$], and a significant group $\times$ session interaction [$F(12, 192) = 3.06$, $P < 0.001$]. Post-hoc tests revealed that all three HAL groups were significantly different from the VEH group (all $P < 0.001$). In addition, the HAL 0.10 group differed significantly from the HAL 0.03 group ($P < 0.001$) but not from the HAL 0.05 group.

Haloperidol sensitization did not transfer to the phencyclidine hyperlocomotion model

Figure 1b shows the mean motor activity of the eight groups of rats during the 60-min test period after saline or PCP injection. One-way ANOVA revealed a significant main effect of group [$F(7, 44) = 4.40$, $P < 0.001$]. Post-hoc Tukey tests showed that in comparison with the VEH-VEH + VEH group, the VEH-VEH + PCP group had a

significantly higher motor activity ($P < 0.001$). This PCP effect was attenuated by HAL pretreatment. In comparison with the VEH-VEH + PCP group, all except HAL 0.10-HAL 0.10 + PCP and VEH-HAL 0.05 + PCP had significantly lower motor activity; all P values were less than 0.05. More importantly, when the pairs of acute and repeated HAL groups were compared (e.g., VEH-HAL 0.05 + PCP vs. HAL 0.05-HAL 0.05 + PCP), no significant difference was found.

Haloperidol sensitization was detected in the conditioned avoidance response model and showed a dose-dependent function

Figure 1c shows the number of avoidance responses during the CS-only, retraining, and sensitization reassessment sessions in the CAR model. In the CS-only session, HAL 0.03 and HAL 0.05 groups still differed significantly from the VEH and HAL 0.10 group, [$F(3, 48) = 8.68$, $P < 0.001$], post-hoc tests with all P values of less than 0.05. These differences disappeared in the retraining session [$F(3, 48) = 0.14$, not significant (NS)]. In the sensitization reassessment test, all rats were tested under HAL 0.03. One-way ANOVA showed a significant effect of group [$F(3, 48) = 7.77$, $P < 0.001$]. Post-hoc tests showed that the HAL 0.10 and HAL 0.05 groups had significantly fewer avoidances than the VEH group ($P < 0.02$ and 0.001 , respectively), which did not differ significantly from the HAL 0.03 group.

Experiment 2: transferability of olanzapine-induced sensitization from the conditioned avoidance response model to the phencyclidine hyperlocomotion model *Repeated olanzapine treatment produced a progressively enhanced disruption of avoidance responding in a dose-dependent manner*

Figure 2a shows the number of avoidance responses made by the rats in the four groups during the five drug sessions. The three OLZ groups showed a progressive across-session decrease in avoidance responding. The VEH group maintained a high level of avoidance responding throughout this phase. Repeated-measures ANOVA showed a significant main effect of group, [$F(3, 49) = 59.48$, $P < 0.001$] and session [$F(4, 196) = 9.46$, $P < 0.001$], but no significant group $\times$ session interaction [$F(12, 196) = 1.44$, NS]. Post-hoc tests revealed that all three OLZ groups were significantly different from the VEH group (all $P < 0.001$). In addition, the OLZ 0.5 group differed significantly from the OLZ 1.0 and OLZ 2.0 groups ($P < 0.05$).

Olanzapine sensitization did not transfer to the phencyclidine hyperlocomotion model

Figure 2b shows the mean motor activity of the eight groups of rats during the 60-min test period after saline or PCP injection. One-way ANOVA revealed a significant main effect of group [$F(7, 49) = 3.41$, $P < 0.005$]. Posthoc tests showed that in comparison with the VEH-

Figure 1. (a) Effect of repeated haloperidol treatment (0.03, 0.05, and 0.10 mg/kg, subcutaneously, – 60 min) on conditioned avoidance responding. Number of avoidance responses made by the rats in the four groups during the five drug conditioning sessions are expressed as mean $\pm$ standard error of the mean. * $P < 0.05$ relative to the vehicle (VEH) group. # $P < 0.05$ relative to the haloperidol (HAL) 0.05 and 1.0 mg/kg groups. (b) Effect of acute haloperidol challenges on phencyclidine-induced hyperlocomotion. Motor activity data are expressed as the mean number of photobeam breaks. Rats were tested for 60 min after phencyclidine (PCP; 1.6 mg/kg, subcutaneously) injection. * $P < 0.05$ relative to the VEH+PCP group. (c) Effect of an acute haloperidol challenge (0.03 mg/kg, subcutaneously, – 60 min) on avoidance responding in rats that were previously treated with haloperidol (0.03, 0.05, and 0.10 mg/kg) or VEH during the sensitization induction phase. The avoidance data on the CS-only and retraining sessions are also presented for comparison. * $P < 0.05$ relative to the VEH group. # $P < 0.05$ relative to the HAL 0.1 mg/kg group. CS, conditioned stimulus.

Figure 2. (a) Effect of repeated olanzapine (OLZ) treatment (0.5, 1.0, and 2.0 mg/kg, subcutaneously, – 60 min) on conditioned avoidance responding. Number of avoidance responses made by the rats in the four groups during the five drug conditioning sessions are expressed as mean $\pm$ standard error of the mean. * $P < 0.05$ relative to the vehicle (VEH) group. # $P < 0.05$ relative to the OLZ 1.0 and 2.0 mg/kg groups. (b) Effect of acute OLZ challenges on phencyclidine (PCP)-induced hyperlocomotion. Motor activity data are expressed as the mean number of photobeam breaks. Rats were tested for 60 min after PCP (1.6 mg/kg, subcutaneously) injection. * $P < 0.05$ relative to the VEH+PCP group. (c) Effect of acute OLZ challenge (0.5 mg/kg, subcutaneously, – 60 min) on avoidance responding in rats that were previously treated with OLZ (0.5, 1.0, and 2.0 mg/kg) or VEH during the sensitization induction phase. The avoidance data on the conditioned stimulus-only and re-training sessions are also presented for comparison. * $P < 0.05$ relative to the VEH group. # $P < 0.05$ relative to the OLZ 0.5 mg/kg group. CS, conditioned stimulus.

VEH + VEH group, the VEH-VEH + PCP group had a significantly higher motor activity ($P < 0.01$). This PCP effect was attenuated by OLZ pretreatment. In comparison with the VEH-VEH + PCP group, VEH-OLZ 2.0 + PCP, $P = 0.004$, and OLZ 2.0-OLZ 2.0 + PCP, $P < 0.02$, had significantly lower motor activity. More importantly, when the pairs of acute and repeated HAL groups were compared (e.g. VEH-OLZ 0.5 + PCP vs. OLZ 0.5-OLZ 0.5 + PCP), no significant difference was found.

Olanzapine sensitization was detected in the conditioned avoidance response model and showed a dose-dependent function

Figure 2c shows the number of avoidance responses during the CS-only, retraining, and sensitization reassessment sessions in the CAR. On the CS-only and retraining days, no significant group difference was found, CS-only [$F(3, 49) = 2.51$, $P = 0.07$], retraining: [$F(3, 52) = 1.44$, NS]. In the sensitization reassessment test, all rats were tested under OLZ 0.5. One-way ANOVA showed a significant effect of group [$F(3, 49) = 10.04$, $P < 0.001$]. Post-hoc tests showed that the OLZ 1.0 and OLZ 2.0 groups, but not the OLZ 0.5 group, had significantly fewer avoidances than the VEH group ($P < 0.002$, $P < 0.001$, and NS, respectively). The OLZ 0.5 group also differed significantly from the other two OLZ groups ($P < 0.05$ vs. OLZ 1.0 and $P < 0.02$ vs. OLZ 2.0).

Experiment 3: transferability of haloperidol-induced sensitization from the phencyclidine hyperlocomotion model to the conditioned avoidance response model

Repeated haloperidol treatment produced a progressively enhanced inhibition of phencyclidine-induced hyperlocomotion

Figure 3a shows the mean motor activity of rats that received HAL 0.05 or VEH treatment during the 60-min daily testing period after PCP injection. Haloperidol treatment progressively enhanced its inhibition of PCP-induced increase in motor activity across the 5 test days. Repeated-measures ANOVA showed significant main effects of group [$F(1, 23) = 71.27$, $P < 0.001$] and session [$F(4, 92) = 8.18$, $P < 0.001$], and a significant group $\times$ session interaction [$F(4, 92) = 7.40$, $P < 0.001$].

Haloperidol sensitization did not transfer to the conditioned avoidance response model

Figure 3b shows the number of avoidance responses on the last (day 10) training day, the retraining day, and the sensitization assessment day (challenge test). All groups had a high level of avoidance response on the 10th training session [$F(2, 22) = 0.11$, NS] and on the retraining day [$F(2, 22) = 1.48$, NS], whereas in the challenge test, the two HAL groups had significantly lower avoidance levels than the VEH group. One-way ANOVA revealed a significant main effect of group, [$F(2, 22) = 9.93$, $P < 0.001$]. Post-hoc Tukey tests showed that both HAL groups differed significantly from the VEH-VEH group ($P < 0.01$).

More importantly, there was no significant difference between the two HAL groups, suggesting that prior HAL experience in the PCP model did not enhance the behavioral effect of HAL in the CAR model.

Haloperidol sensitization was present in the phencyclidine hyperlocomotion model

Figure 3c shows the mean motor activity 30 min before and 60 min after PCP injection during the sensitization reassessment test. All rats received a first injection of HAL 0.03, followed by PCP 3.2. In comparison with the VEH rats that received HAL for the first time in this model, rats that had previously received HAL 0.05 (Figure 3a) exhibited significantly lower motor activity in the first 30 min [$t(23) = -2.92$, $P = 0.01$], and the second 60 min [$t(23) = -3.21$, $P = 0.005$].

Experiment 4: transferability of olanzapine-induced sensitization from the phencyclidine hyperlocomotion model to the conditioned avoidance response model

Repeated olanzapine treatment produced a progressively enhanced inhibition of phencyclidine-induced hyperlocomotion

Figure 4a shows the mean motor activity of rats that received olanzapine 1.0 or VEH treatment during the 60-min daily testing period after PCP injection. Olanzapine treatment progressively enhanced its inhibition of PCP-induced increase of motor activity across the 5 test days. Repeated-measures ANOVA showed significant main effects of group [$F(1, 24) = 40.65$, $P < 0.001$] and session [$F(4, 96) = 3.18$, $P < 0.02$], and a significant group $\times$ session interaction [$F(4, 96) = 9.06$, $P < 0.001$].

Olanzapine sensitization did not transfer in the conditioned avoidance response model

Figure 4b shows the number of avoidance responses on the last (day 10) training day, retraining day, and on the sensitization assessment day (challenge test). All groups had a high level of avoidance response on the 10th training session [$F(2, 23) = 0.558$, NS] and on the retraining day [$F(2, 23) = 0.44$ NS], whereas in the challenge test, the two OLZ groups had lower avoidance levels than the VEH group. One-way ANOVA revealed a significant main effect of group [$F(2, 23) = 4.24$, $P < 0.05$]. Post-hoc Tukey tests showed that the OLZ 1.0-0.5 group differed significantly from the VEH-VEH group ($P = 0.026$). Acute OLZ 0.5 decreased the avoidance response, but the effect did not reach a significant level. Most importantly, there was no significant difference between the two OLZ groups, suggesting that prior OLZ experience in the PCP model did not enhance the behavioral effect of OLZ in the CAR model. However, the finding that only the OLZ 1.0-0.5 group, but not the VEH-OLZ 0.5 group, differed significantly from the VEH-VEH group indicates that there might be some residual effect of OLZ experience, which requires further verification.

Figure 3. (a) Effect of repeated haloperidol treatment (0.05 mg/kg, subcutaneously) on phencyclidine (PCP)-induced hyperlocomotion. Motor activity data are expressed as the number of photobeam breaks. Rats were tested for 60 min after PCP (3.2 mg/kg, subcutaneously) injection. * $P < 0.05$ relative to the vehicle (VEH)+PCP group. (b) Number of avoidance responses made by the rats in the three groups during the 10th training, retraining, and CS-only test sessions (under an acute haloperidol challenge, 0.03 mg/kg, subcutaneously, – 60 min) are expressed as mean $\pm$ standard error of the mean. * $P < 0.05$ relative to the VEH group. (c) Effect of acute haloperidol challenge (0.03 mg/kg, subcutaneously) on PCP-induced hyperlocomotion during the sensitization reassessment test. Motor activity data are expressed as the number of photo beam breaks. Rats were tested for 30 min (T30) before and 60 min (T60) after PCP (3.2 mg/kg, subcutaneously) injection. * $P < 0.05$ relative to the VEH group. CS, conditioned stimulus.

Olanzapine sensitization was present in the phencyclidine hyperlocomotion model

Figure 4c shows the mean motor activity in the 30 min before and 60 min after PCP injection during the sensitization reassessment test. All rats received a first injection of OLAN 0.5, followed by PCP 3.2. In comparison with the VEH rats that received olanzapine for the first time in this model, rats that had previously received OLAN 1.0 (Figure 4a) exhibited significantly lower motor activity in the first 30 min [$t(24) = -3.19$, $P < 0.005$], and

significantly lower motor activity in the second 60 min [$t(24) = -3.71$, $P < 0.001$].

Discussion

Our findings on antipsychotic sensitization induced by HAL and OLAN in both CAR and PCP hyperlocomotion models are consistent with our previous studies, in which we showed that repeated HAL and OLAN treatment

Figure 4. (a) Effect of repeated olanzapine (OLZ) treatment (1.0 mg/kg, subcutaneously) on phencyclidine (PCP)-induced hyperlocomotion. Motor activity data are expressed as number of photobeam breaks. Rats were tested for 60 min after PCP (3.2 mg/kg, subcutaneously) injection. * $P < 0.05$ relative to the vehicle (VEH)+PCP group. (b) Number of avoidance responses made by the rats in the three groups during the 10th training, retraining, and conditioned stimulus-only test sessions (under an acute olanzapine challenge, 0.5 mg/kg, subcutaneously, – 60 min) are expressed as mean $\pm$ standard error of the mean. * $P < 0.05$ relative to the VEH group. (c) Effect of acute OLZ challenge (0.5 mg/kg, subcutaneously) on PCP-induced hyperlocomotion during the sensitization reassessment test. Motor activity data are expressed as number of photo beam breaks. Rats were tested for 30 min (T30) before and 60 min (T60) after PCP (3.2 mg/kg, subcutaneously) injection. * $P < 0.05$ relative to the VEH group.

caused a progressive and persistent increase in their effects on avoidance responding and PCP-induced hyperlocomotion (Li *et al.*, 2004b, 2007, 2009a, 2009b, 2010; Mead and Li, 2010). One unique aspect of this study is that two distinct animal models of antipsychotic drugs were utilized to examine the phenomenon of antipsychotic sensitization and its contextual and behavioral controls. The lack of transfer of sensitization was found in both directions and with both drugs, suggesting that it is a general

feature of antipsychotic action, rather than an artifact of any specific models or drugs.

The present study extended our work in the following four directions. First, it showed that antipsychotic sensitization in the PCP hyperlocomotion model could also be assessed in the same way as in the CAR model, which is also the typical setup used to assess psychomotor sensitization (Anagnostaras and Robinson, 1996; Pierce and Kalivas, 1997; Robinson *et al.*, 1998). That is, the expres-

sion of antipsychotic sensitization could be examined in a later challenge test during which all subjects are tested under the same antipsychotic drug treatment. The behavioral sensitization is indicated by the higher inhibition in the antipsychotic experienced group than in the drug-naïve group. In our previous studies, antipsychotic-induced sensitization was only indicated by the progressively enhanced inhibition of PCP-induced hyperlocomotion during the repeated drug-treatment period (Sun *et al.*, 2009). The commonality among these different types of sensitization (e.g. psychomotor sensitization and antipsychotic sensitization) implies that many research techniques, approaches, and knowledge derived from psychomotor sensitization studies might be introduced into the study of antipsychotic sensitization.

Second, the study provided a novel approach to assess the situational specificity of antipsychotic sensitization. Studies on contextual and behavioral controls of psychomotor sensitization or tolerance typically compare a "paired" group (a group that receives drug injection in the test environment) with an "unpaired" group (a group that receives VEH injection in the test environment, and drug in the home cage) in a single model (Poulos and Hinson, 1982; Amtage and Schmidt, 2003). The situational specificity of psychomotor sensitization is indicated by the finding that it is expressed only in the "paired" group but not in the "unpaired" group (Robinson *et al.*, 1998). Our previous work used a similar approach and demonstrated that within the CAR model, antipsychotic sensitization was indeed context dependent (Li *et al.*, 2009a). We found that rats that received HAL (0.05 mg/kg) or OLZ (1.0 mg/kg) and tested for avoidance (i.e., the "paired" group) exhibited a progressive enhanced decrease in avoidance responding, indicative of the antipsychotic sensitization effect, whereas rats that received these drugs in their home cages but tested for avoidance under VEH (i.e., the "unpaired" group) did not. The present study suggested that it is useful to use two different behavioral models to assess the situational specificity of antipsychotic sensitization. In comparison with the traditional one-model approach, this two-model approach is advantageous in revealing multiple sources of controls of antipsychotic sensitization. Besides distinctive contextual cues, topographically different behavioral response patterns (i.e., avoidance response to a sound and PCP-induced increase in motor activity) certainly play a role in this process (Ohmori *et al.*, 2000). This may explain the rather robust and complete situational control of antipsychotic sensitization in this study. However, one limitation of this approach is its inability to determine the relative contributions of contextual cues and behavioral responses toward the development and expression of antipsychotic sensitization. Future work utilizing both approaches is needed to address this question.

Third, the study extended the context-dependent sensitization phenomenon involving antipsychotics from

HAL-induced catalepsy (Lanis and Schmidt, 2001; Amtage and Schmidt, 2003; Klein and Schmidt, 2003) to subject behavioral responses relevant to human psychosis and to other antipsychotic drugs. Amtage and Schmidt (2003) and Klein and Schmidt (2003) have reported that intermittent HAL treatment and repeated catalepsy testing caused an intensification of catalepsy over time and this intensification was completely context specific, as context changes abolished catalepsy sensitization. In the present study, we demonstrated that sensitization induced by the atypical drug OLZ in the CAR and PCP hyperlocomotion models was also highly situation specific, suggesting that this feature of antipsychotic sensitization may cut across different groups of antipsychotic drugs and may be a universal feature reflecting the therapeutic effects of antipsychotic drugs.

Finally, this study called attention to the issue of possible connections among various animal models of antipsychotic drug action. In preclinical psychopharmacology, there are many diverse groups of animal models of antipsychotic activity, such as prepulse inhibition of acoustic startle, latent inhibition, amphetamine-induced and PCP-induced hyperlocomotion, the paw test, and so on (Weiner and Feldon, 1994; Kilts, 2001; Geyer and Ellenbroek, 2003). Often, these models are utilized independently without much attention paid to their possible relationships. As they all claim to be able to detect antipsychotic activity, one important issue is how they are related and whether it is possible to use one model to cross-validate another. The present study suggests a way to explore this issue.

As the context-dependent feature of antipsychotic sensitization resembles that found in psychomotor sensitization (Vezina *et al.*, 1989; Stewart and Vezina, 1991; Anagnostaras and Robinson, 1996; Browman *et al.*, 1998; Robinson *et al.*, 1998; Anagnostaras *et al.*, 2002) and tolerance (Siegel, 1978; Poulos *et al.*, 1981; Siegel *et al.*, 2000), the conceptualization of antipsychotic sensitization and its situational specificity can gain insights from the theoretical accounts of behavioral sensitization and tolerance. On the basis of the present study, our previous work (Li *et al.*, 2004b, 2007, 2009a, 2009b, 2010; Mead and Li, 2010) and the work of others (Stewart and Vezina, 1991; Anagnostaras *et al.*, 2002), we propose that three psychological and neuronal processes may govern the induction and expression of antipsychotic sensitization and its contextual and behavioral controls.

First, repeated antipsychotic treatment may induce an unconditioned and nonassociative enhancement of behavioral effects (i.e., sensitization) attributable to the direct pharmacological action of a drug. There is substantial evidence indicating that chronic antipsychotic treatment alters the neurochemical systems that mediate their behavioral activating effects (Meltzer *et al.*, 1989; Konradi and Heckers, 2001; Meltzer *et al.*, 2003; Schmitt *et al.*, 2003; Lieberman *et al.*, 2008). Many antipsychotic sensitization-related brain changes have been identified

and they are observed in the absence of any associative influence. For example, it has been shown that repeated antipsychotic treatment changes the density and sensitivity of dopamine D₂ receptors (Seeman, 2000; Samaha *et al.*, 2007, 2008), 5-HT_{2A} and 5-HT_{2C} receptors (Buckland *et al.*, 1997) and other receptors (McCoy *et al.*, 1996; Marcus *et al.*, 1997; Nudmamud and Reynolds, 2001; Tooney *et al.*, 2005). Our own work on the neurochemical basis of the antipsychotic sensitization induction in the CAR model also indicates a role for dopamine and serotonin receptors in this process (Li *et al.*, 2010, 2011b). We found that with 2,5-dimethoxy-4-iodo-amphetamine, a selective 5-HT_{2A/2C} serotonergic receptor agonist, but not quinpirole, a selective D₂/D₃ dopaminergic receptor agonist, attenuated HAL sensitization of avoidance responding, whereas pretreatment with quinpirole, but not 2,5-dimethoxy-4-iodo-amphetamine, attenuated the effect of OLZ. These findings suggest that the induction of HAL sensitization may be mediated by 5-HT_{2A/2C} blockade-initiated neuroplasticity, whereas the induction of OLZ sensitization may be mediated by D₂/D₃ blockade-initiated neuroplasticity. Psychologically, our previous work suggests that antipsychotic drugs disrupt avoidance responding by progressively attenuating the motivational salience of the CS (Li *et al.*, 2007). This hypothesis can also be utilized to explain the sensitization effect in the PCP hyperlocomotion model. The PCP model can be thought of as reflecting an exaggerated exploration of the environment as a consequence of the increased motivational salience of environmental stimuli (Wise and Bozarth, 1987). Therefore, the antipsychotic-induced progressively enhanced inhibition of PCP-induced hyperlocomotion can be considered a consequence of the weakened motivational salience of environmental stimuli by antipsychotic treatment.

Second, distinct contextual cues (e.g. environmental stimuli, interoceptive drug cue, etc.) and altered behavioral responses in each model may develop an association with unconditional drug effects through a Pavlovian conditioning process, and thus become excitatory conditional stimuli. These contextual cues and behavioral variables acquire the ability to elicit an antipsychotic-like effect by themselves and may potentiate the sensitized response in an expected situation. The lack of transfer of sensitization between models could be attributed to the disruption of the excitatory controls of contextual cues and behaviors, as the across-model transfer entails changes not only in context but also in behavioral responses. Contextual changes may consist of stimulus addition (inclusion of novel contextual stimuli) as well as stimulus subtraction (loss of originally trained context). Substantial evidence suggests that contextual cues, especially the environmental stimuli and interoceptive drug state, can serve as conditional stimuli and become associated with unconditional drug effects (as US) by a Pavlovian conditioning process after being repeatedly paired with a drug (Siegel *et al.*, 2000). In our

own lab, we have shown that rats that had been repeatedly treated with HAL (0.05 mg/kg, subcutaneously) and clozapine (20 mg/kg, subcutaneously) during the acquisition or the extinction phase of the CAR model still showed a decreased avoidance response when they were tested 2 days later in the absence of the drug (Li *et al.*, 2004b). In the present study, we also observed that rats previously treated with HAL (0.03 and 0.05 mg/kg) made fewer avoidance responses on the CS-only drug-free test. These findings imply that the CAR testing environment exerted an antipsychotic-like effect on avoidance responding. Future work is needed to specify the magnitude of the impact of contextual cues on antipsychotic sensitization.

Finally, contextual stimuli and different topographic behavioral responses may serve as occasion setters to modulate the manifestation of sensitized responses. Occasion setters are a class of conditional stimuli that do not themselves elicit an antipsychotic-like effect, but modulate the ability of other stimuli to elicit responses (Holland, 1989). A change of testing models may cause a disruption of the occasion-setting property of contextual stimuli and behavioral responses, which leads to the disruption of across-model transfer of antipsychotic sensitization. It is well documented that contextual cues and altered behavioral responses can function as occasion setters to modulate the expression of psychomotor sensitization involving psychostimulants (Smith, 1991; Anagnostaras and Robinson, 1996; Lanis and Schmidt, 2001; Sripada *et al.*, 2001). Our previous work also provides evidence supporting this account. For example, in the study by Mead and Li (2010), we showed that rats intermittently treated with OLZ (1.0 mg/kg, subcutaneously) or HAL (0.03 mg/kg, subcutaneously) on the first day of a 3-day cycle for seven cycles exhibited a progressive across-session decline in avoidance responding (i.e., antipsychotic sensitization), despite the fact that they exhibited a comparable high level of avoidance responding on the third day of each cycle during the drug-free retraining session. As we have previously discussed (Mead and Li, 2010), an antipsychotic drug and altered behavioral responses can act as an occasion setter (Maes and Vossen, 1997), which sets the condition in which rats behave on the basis of their previous drug experience in the avoidance testing context, or it may directly imprint the brain to create a drug "memory trace" about avoidance responding under drug (the neural basis of antipsychotic sensitization). One prediction on the basis of this drug-dependent sensitization mechanism is that even if the drug has been stopped and the avoidance responding has fully reverted to the predrug level, during the next exposure to antipsychotic treatment, the subjects with a previous drug experience should show a greater response, a prediction that was confirmed for both OLZ and risperidone (Mead and Li, 2010).

In summary, the present study used a novel two-model approach and provided strong evidence for the

contextual and behavioral controls of antipsychotic sensitization. Our work also revealed three neuropsychological processes that are potentially critical for the induction and expression of antipsychotic sensitization, emphasizing the long-term neuroplasticities due to chronic drug treatment and the role of contextual cues and behaviors functioning as conditional stimuli and occasion setters. Insofar as this effect is important for maintaining antipsychotic effects over time, understanding the neurobiological and psychological mechanisms behind it would greatly enhance our knowledge of the psychological and neurochemical nature of antipsychotic treatment in the clinic.

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