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# Effects of repeated quetiapine treatment on conditioned avoidance responding in rats

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## Abstract

The present study characterized the behavioral mechanisms of avoidance–disruptive effect of quetiapine in the conditioned avoidance response test under two behavioral testing (2 warning signals vs. 1 warning signal) and two drug administration conditions (subcutaneous vs. intravenous). In Experiments 1 and 2, well-trained adult male Sprague–Dawley rats were tested under the subcutaneous (s.c.) quetiapine treatment (5.0, 15.0, 25.0, 50.0 mg/kg) for 7 days in a novel procedure consisting of two conditioned stimuli (CS) (white noise serving as CS1 and pure tone as CS2). Only the highest dose (50.0 mg/kg) produced a persistent suppression of the avoidance response without impairing the escape response. The magnitude of suppression of the CS1 avoidance was similar to that of CS2 avoidance. No significant group difference was found in the quetiapine (15.0 mg/kg, s.c.) challenge test, indicating a lack of a long-term quetiapine effect. In Experiment 3, well-trained rats were tested under the intravenous (i.v.) quetiapine treatment (3.0, 9.0, 15.0 mg/kg) for 5 days and challenged with quetiapine (6.0 mg/kg, i.v. followed by 9.0 mg/kg, s.c.). Only the white noise was used as the CS. Similar to what was being observed in Experiments 1 and 2, intravenously administered quetiapine dose-dependently suppressed avoidance responding during the drug test days, but did not alter drug sensitivity in the challenge days. Thus, quetiapine does not appear to show a preferential inhibition of the avoidance response to a less salient stimulus; and prior quetiapine treatment (s.c. and i.v.) does not cause a sensitization or tolerance to quetiapine.

**Keywords:** Quetiapine, CS1 and CS2, Conditioned avoidance response, Sensitization, Tolerance

## 1. Introduction

The conditioned avoidance response model (CAR) is a classic behavioral screening tool for chemical compounds with antipsychotic activity, as avoidance suppression is a common and distinct property of antipsychotic drugs but not that of other psychotropic drugs. This task is also useful for the study of the behavioral mechanisms of antipsychotic action (Li et al., 2007, 2009a, 2009b, 2004, 2010, 2012; Mead and Li, 2010; Swalve and Li, 2012). In this regard, we have shown that antipsychotic drugs suppress avoidance response by attenuating the motivational salience of a conditioned stimulus (CS) to elicit avoidance response. The attenuation action on the motivational salience of the CS refers to the weakening effect of antipsychotic treatment on the ability of the CS to instigate an active motor response from an organism. We demonstrated

that the avoidance–disruptive effect of haloperidol, olanzapine and clozapine can be potentiated by the increase in number of CS trials in the test sessions (Feng et al., 2012; Li et al., 2007). Furthermore, both clozapine and olanzapine show a greater suppression of the avoidance response to a less salient CS than to a more salient CS (Li et al., 2009b, 2012; Zhang et al., 2011). We also identified another behavioral mechanism which relates to the drug-induced alteration of drug sensitivity. We showed that repeated treatment with haloperidol, olanzapine or risperidone daily for 5–7 days tends to cause a progressively increased inhibition of avoidance responding (a sensitization effect), while repeated administration of clozapine causes a decreased inhibition upon repeated administration (a tolerance effect) (Feng et al., 2013b; Li et al., 2010, 2012; Qiao et al., 2013). These findings are consistent with earlier studies showing that the anti-avoidance effect of haloperidol is

progressively enhanced with each subsequent drug administration (Fregnan and Chieli, 1980), while that of clozapine is progressively decreased (Sanger, 1985).

The present study was designed to examine the behavioral mechanisms of action of quetiapine in the CAR model. Specifically, we attempted to determine whether quetiapine disrupts avoidance response by attenuating the motivational salience of the CS and induces a long-term change in drug sensitivity (either sensitization or tolerance). Quetiapine is a widely used atypical antipsychotic drug that is effective in the treatment of schizophrenia, bipolar disorders and other mental disorders (Zhornitsky et al., 2011). It is also used as an adjuvant treatment for major depressive disorder and those who did not have an adequate response to antidepressant therapy (Bandelow et al., 2014; Sanford, 2011). Although its avoidance disruptive effect has been demonstrated before (Bjorkholm et al., 2013; Wadenberg et al., 2001), how quetiapine disrupts avoidance response and what kind of behavioral pattern (sensitization or tolerance) it would induce has never been studied. Since quetiapine exhibits clozapine-like lower levels of dopamine  $D_2$  receptor occupancy (less than 70%) at therapeutically effective doses and a clozapine-like fast dissociation from the  $D_2$  receptor (Kapur and Seeman, 2000; Kapur et al., 2000), we hypothesized that repeated treatment of quetiapine would cause a clozapine-like tolerance effect (as opposed to olanzapine-like sensitization) in the CAR model. To examine its potential action on the motivational salience of the CS, we tested quetiapine in a modified CAR paradigm involving two types of CS signals with different levels of motivational salience (Li et al., 2009b, 2012, Zhang et al., 2011).

## 2. Materials and methods

### 2.1. Animals

In Experiment 1, 50 adult male drug-naïve Sprague-Dawley rats (226–250 g upon arrival, Charles River, Portage, MI) were used as subjects. In Experiment 2, 40 adult Sprague-Dawley rats (226–250 g upon arrival) that had been previously used in another study were used. These rats had been repeatedly injected with saline, nicotine 0.2 mg/kg, or nicotine 0.4 mg/kg, in combination with saline or phencyclidine (2.0 mg/kg) for 7 days, and tested for the ultrasonic vocalization under PCP and/or nicotine. However, none of them had any experience with quetiapine. We used them in this study in an attempt to replicate findings from Experiment 1. Because they had different drug experience compared to rats used in Experiment 1, the consistent findings from both experiments would enhance the confidence of our findings. In Experiment 3, 46 adult male drug-naïve Sprague-Dawley rats (226–250 g upon arrival) were used. Rats were housed two per cage, in transparent polycarbonate cages (48.3 × 26.7 × 20.3 cm) under 12-hr 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 was available *ad libitum*. Animals were allowed at least 5 days of habituation to the animal facility before being used in experiments. All experiments were performed during the light cycle and all procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska–Lincoln.

### 2.2. Drugs

Quetiapine fumarate (QUE, a gift from the National Institute of Mental Health drug supply program) was dissolved in a minimal amount (up to 1.5%) of glacial acetic acid and made up to volume with distilled sterile water (Kapur et al., 2003 and Wadenberg et al., 2001), and injected subcutaneously (s.c., 1.0 ml/kg) in Experiments

1 and 2. For Experiment 3, QUE was dissolved in a minimal amount of acetic acid (up to 1%) and diluted to the appropriate concentration with saline (0.9% NaCl solution), the pH was raised slightly by adding of a few drops of 1 N NaOH and injected intravenously (i.v., 1.0 ml/kg) into a lateral tail vein (Bjorkholm et al., 2013). We tested a wide range of QUE doses (3–50 mg/kg) to assess the possible dose-dependent nature of QUE effects. QUE is shown to suppress avoidance response at >20 mg/kg s.c. and >6.0 mg/kg i.v. (Bjorkholm et al., 2013 and Wadenberg et al., 2001).

### 2.3. Two-way avoidance conditioning apparatus

Eight identical two-way shuttle boxes custom designed and manufactured by Med Associates (St. Albans, VT) were used. Each box was housed in a ventilated, sound-insulated isolation cubicle (96.52 cm W × 35.56 cm D × 63.5 cm H). 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 footshock (unconditioned stimulus, US, 0.8 mA,) was delivered by a constant current shock generator (Model ENV-410B) and scrambler (Model ENV-412). The rat 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 houselights mounted at the top of each compartment. The auditory stimuli were generated by a programmable audio generator (ANL-926) and delivered by the speaker (ENV-224AM). In Experiments 1 and 2, a 76 dB white noise (the sound frequency ranged from 10 to 35,000 Hz in 1 Hz increment, serving as CS1) and an 85 dB 2800 Hz pure tone (serving as CS2) were used. In Experiment 3, only the white noise was used. Both sounds were 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.

### 2.4. Experiment 1: Effect of repeated QUE treatments on CS1 and CS2 avoidance in normal rats

Fifty rats were first handled and habituated to the CAR boxes for 2 days (20 min/day), and then trained to make avoidance responses to the white noise (CS1) for a total of 10 days/sessions over a 2-week period. Each session consisted of 30 trials, with inter-trial intervals randomly varying between 30 and 60 s. Every trial started with the presentation of white noise for 10 s, followed by a continuous scrambled foot shock (0.8 mA, US, maximum duration = 5 s) on the grid floor. An avoidance response was registered if a rat crossed from one compartment into the other within the 10 s of CS1 presentation. An escape was registered if the rat remained in the same compartment for more than 10 s and made a crossing only after receiving the footshock. If the rat did not switch compartments during the entire 5 s presentation of the shock, the trial was terminated and the inter-trial interval started.

At the end of the training session, 42 rats reached the training criterion (>70% CS1 avoidance in each of the last 2 sessions). They were first matched on avoidance performance on the last training day (pre-drug) to create blocks of rats that were approximately equal in performance. Within each block, they were then randomly assigned to 1 of 5 groups: QUE 5.0 mg/kg ( $n=8$ ),

QUE 15.0 mg/kg ( $n=8$ ), QUE 25.0 mg/kg ( $n=10$ ), QUE 50.0 mg/kg ( $n=8$ ), and vehicle ( $n=8$ ), and tested daily in a modified avoidance response test procedure for 7 consecutive days. On each test day, rats were first injected with QUE or vehicle (sterile water), and tested 1 h later. Each test session consisted of 30 trials with 20 CS1 trials intermixed with 10 CS2 (pure tone) trials. The CS1 trials were identical to the trials used in the training phase. The 10 CS2 trials used a pure tone (10 s, 2800 Hz, 85 dB) as the signal with its termination immediately followed by the shock if the rats did not make an avoidance response (Li et al., 2009b, Li et al., 2012 and Zhang et al., 2011). This modified avoidance test procedure provides a condition to delineate the strength of the avoidance disruptive effect of QUE.

One day after the last CAR drug test, all rats were retrained drug-free under the CS-only condition (20 CS1 trials and 10 CS2 trials) for one session, and under the CS-US condition (20 CS1 trials and 10 CS2 trials) for another session to bring their avoidance back to the pre-drug level. A final challenge test was conducted 24 h later during which all rats were injected with QUE 15.0 mg/kg, and 1 h later, tested for avoidance performance under the CS-only condition (20 CS1 trials and 10 CS2 trials), as previously employed (Li et al., 2012). Table 1 summarizes the experimental procedure.

### 2.5. Experiment 2: effect of repeated QUE treatments on CS1 and CS2 avoidance in nicotine and PCP pretreated rats

In this experiment, we replicated Experiment 1 by testing QUE in 40 rats that were previously treated with nicotine and PCP. The PCP-pretreated rats were used here as “diseased” rats, as PCP is commonly used to induce changes resembling schizophrenia at multiple levels, such as abnormality of glutamatergic neurotransmission and neurodevelopment (Mouri et al., 2007), neuropsychological deficits (Javitt and Zukin, 1991), and prepulse inhibition deficit (Geyer et al., 2001). Our previous study showed that this PCP treatment regimen does cause a disruption of PPI (Li et al., 2011), thus, this experiment extended the study of QUE’s antipsychotic effects in normal rats to rats with schizophrenia-like symptoms. Rats were first trained to acquire CS1 avoidance responding for 10 sessions. At the end of the training phase, 34 rats had reached the training criterion ( $>70\%$  avoidance in each of the last 2 sessions). They were then semi-randomly assigned to 1 of 5 groups (matched by their avoidance performance and their previous experience with nicotine and PCP): QUE 5.0 mg/kg ( $n=6$ ), QUE 15.0 mg/kg ( $n=7$ ), QUE 25.0 mg/kg ( $n=6$ ), QUE 50.0 mg/kg

kg ( $n=8$ ), and vehicle ( $n=7$ ). The remainder of the experimental procedure was identical to that of Experiment 1.

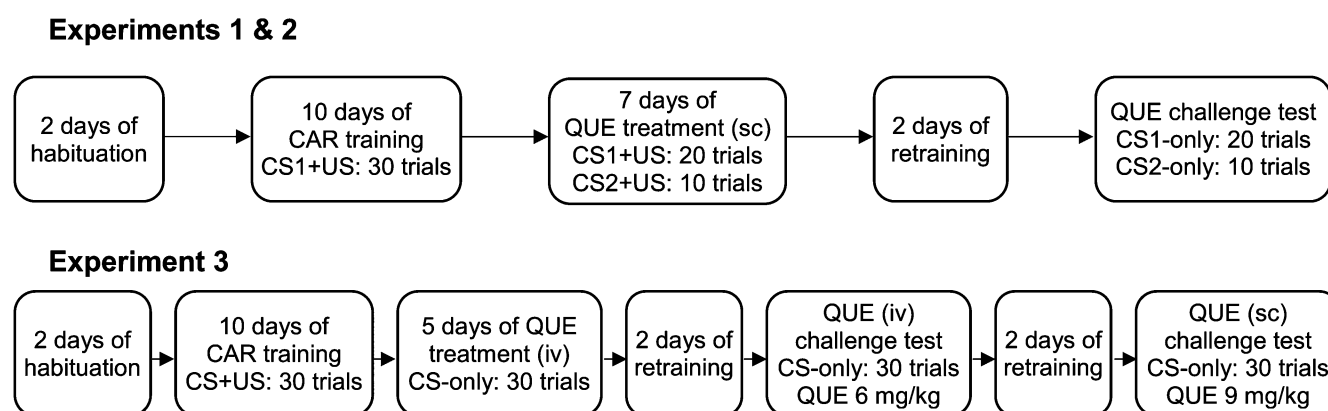
### 2.6. Experiment 3: effect of repeated QUE treatments (i.v.) on conditioned avoidance in normal rats

To circumvent the first-pass metabolism (Pond and Tozer, 1984) and skin lesions produced by s.c. injection, we used the intravenous route of administration in this experiment. This change in injection route would provide a more complete picture of the behavioral effects of QUE. In this experiment, 46 rats were trained in the same procedure as those in the previous experiments. At the end of the training session, 36 rats acquired a robust avoidance responding ( $\geq 70\%$  avoidance in each of the last 2 sessions). They were matched on the level of avoidance and then randomly assigned into 4 groups ( $n=8-10$ /group): vehicle ( $n=9$ ), QUE 3.0 mg/kg ( $n=9$ ), QUE 9.0 mg/kg ( $n=8$ ), QUE 15.0 mg/kg ( $n=10$ ). They were then tested daily under the CS (white noise)-only condition (no shock, 30 trials/session) for 5 consecutive days. This procedure has been routinely used in our studies of antipsychotic sensitization and tolerance (Feng et al., 2013a, Feng et al., 2013b, Gao and Li, 2013, Gao et al., 2015, Swale and Li, 2012 and Zhang and Li, 2012). On each test day, rats were first injected with vehicle (VEH) or QUE in a lateral tail vein (i.v.) and tested in the CAR boxes 20 min later. One day after the last (5th) drug test day, all rats were retrained drug-free for 1 session under the CS-only (no shock) condition, followed by another under the CS-US condition to bring their avoidance responses back to the pre-drug level. On the challenge day, all rats were injected with QUE at 6.0 mg/kg (i.v.) and tested for avoidance performance in the CS-only condition (30 trials) 20 min later. One day after this challenge test, all rats were once again retrained for 2 sessions (1 under the CS-only and 1 under the CS-US condition), followed by another QUE (9.0 mg/kg, s.c.) challenge test 1 day later (see Table 1).

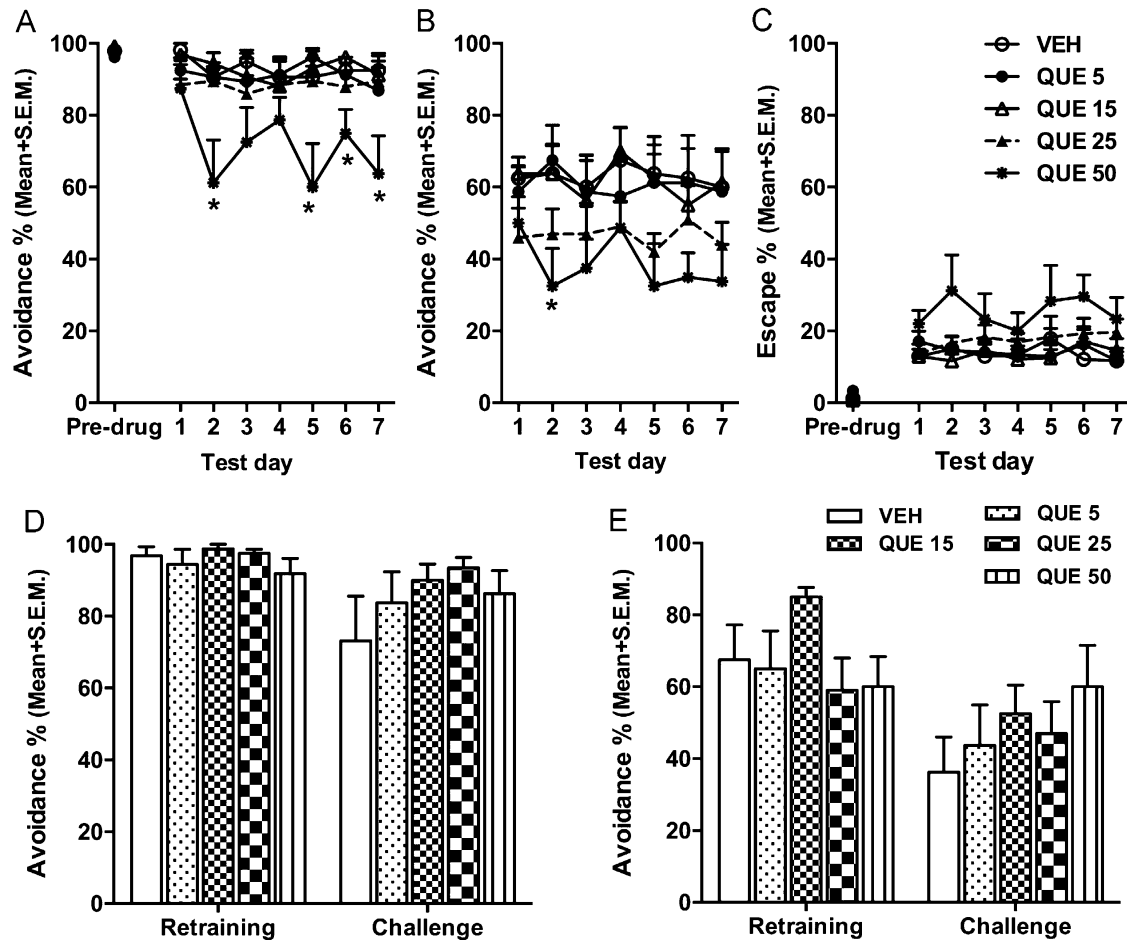
### 2.7. Statistical analysis

Avoidance and escape performance was expressed as the mean percent  $\pm$  S.E.M. (i.e. number of avoidance or escape response/total number of trials). Avoidance data from the repeated drug test days and the challenge test were analyzed using a split-plot analysis of variance (ANOVA) with the between-subjects factor of drug group, and the within-subjects factor of test day and CS condition (CS1 or CS2) (only for Experiments 1 and 2). Escape data was similarly analyzed with the exception of no CS condition as a within-subject

**Table 1.** A schematic depiction of the experimental procedures used in Experiments 1, 2 and 3. QUE: quetiapine; CS: conditioned stimulus; US: unconditioned stimulus.







**Figure 1.** Effect of repeated subcutaneous administration of quetiapine (5, 15, 25 and 50 mg/kg, sc, -60 min) on CS1 – (A) and CS2 (B) – elicited avoidance response and escape response (C) during the 7 drug test days, and its effect on the CS1 – (D) and CS2 – (E) avoidance response on the quetiapine challenge day (quetiapine 15 mg/kg, s.c.) in normal rats. Percentages of avoidance or escape response (mean ± S.E.M.) made by normal rats in the 5 groups on the last training day (pre-drug) and during the 7 drug test days, on the last retraining (drug-free) day and the quetiapine challenge day are shown. \* $P < 0.05$  in comparison to the vehicle group.

factor. One-way ANOVAs followed by post-hoc LSD tests were used to compare group differences on specific drug test days and challenge days. For all comparisons, significant difference was assumed at  $P < 0.05$ , and all data was analyzed using SPSS version 21.

### 3. Results

#### 3.1. Experiment 1: Effect of repeated subcutaneous administration of QUE on CS1 and CS2 avoidance in normal rats

##### 3.1.1. Avoidance response during the drug treatment days

Figure 1(A and B) shows the mean percentage of CS1 avoidance (A) and CS2 avoidance (B) on the last training (pre-drug) day and throughout the 7 drug test days. On the pre-drug day, there were no significant group differences [ $F(4,37) = 0.952$ ,  $P = 0.445$ ]. Throughout the QUE test phase, rats made a higher percentage of CS1 avoidances than CS2 avoidances. Only QUE 50 mg/kg showed an apparent disruption of avoidance responses. A split-plot ANOVA indicated a main effect of group [ $F(4,37) = 3.645$ ,  $P = 0.013$ ], a main effect of CS condition [ $F(1,37) = 262.331$ ,  $P < 0.001$ ], but no main effect of day [ $F(6,222) = 1.296$ ,  $P = 0.260$ ], nor any significant interactions (all  $P > 0.284$ ). Post-hoc Fisher's LSD tests showed that the QUE 50 group had significant lower avoidance than the vehicle group ( $P = 0.003$ ). It also had significantly lower avoidance than other QUE groups (all  $P < 0.007$ ) except the QUE 25

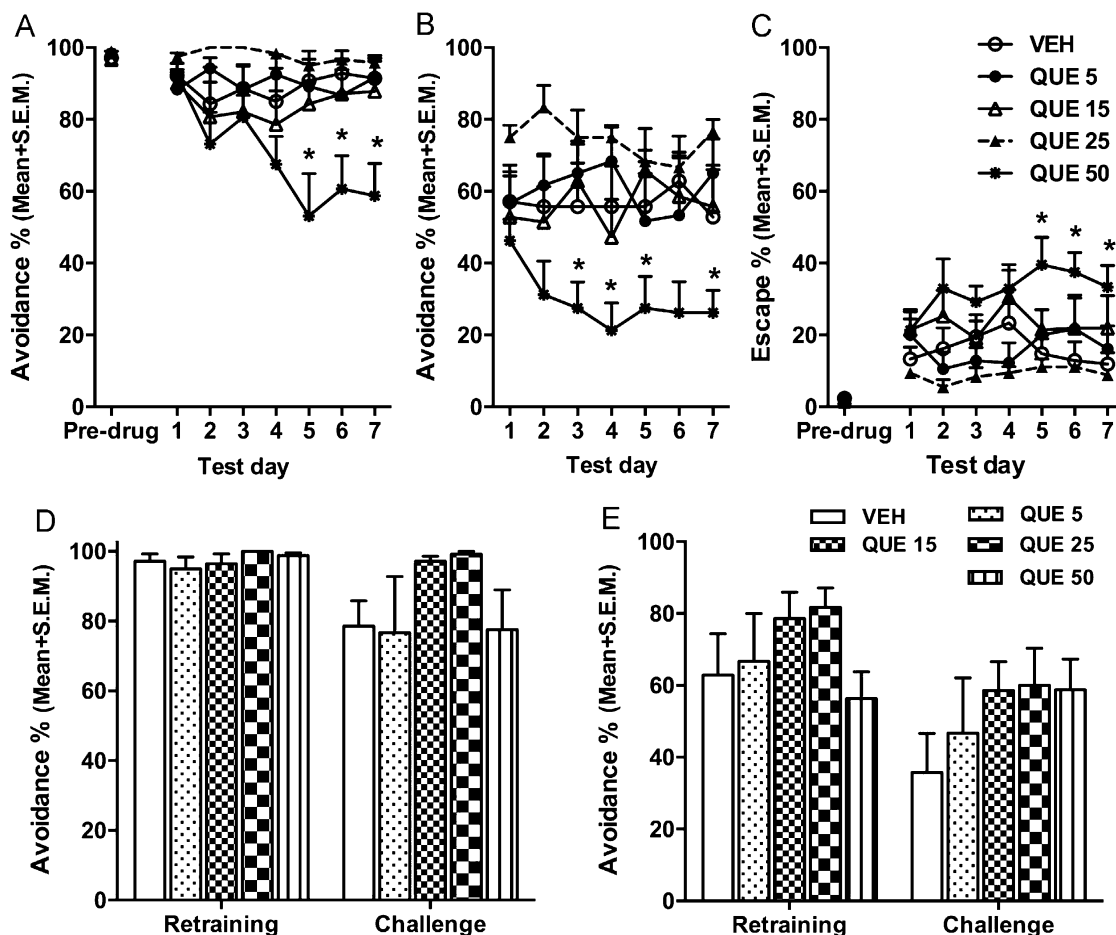
group ( $P = 0.075$ ). One-way ANOVAs followed by post-hoc Fisher's LSD tests on each test day revealed that the QUE 50 group had significantly lower CS1 avoidance percentages than the VEH group on day 2,  $P = 0.002$ , day 5,  $P = 0.002$ , day 6,  $P = 0.011$ , and day 7,  $P = 0.008$ ; and significantly lower CS2 avoidance percentage than the VEH group on day 2,  $P = 0.017$  (Figure 1B). These findings demonstrated that only the high-dose of QUE (50.0 mg/kg) was able to cause a persistent suppression of avoidance responses to CS1 (less to CS2) across the drug test sessions.

##### 3.1.2. Escape response during the drug treatment days

Figure 1C shows the mean percentage of total escape responses on the last training (pre-drug) day and throughout the 7 drug test days. On the pre-drug day, there were no significant group differences [ $F(4,37) = 1.129$ ,  $P = 0.358$ ]. A split-plot ANOVA indicated that throughout the QUE test phase, there was no main effect of day [ $F(6,222) = 1.252$ ,  $P = 0.281$ ], group [ $F(4,37) = 1.950$ ,  $P = 0.123$ ], nor a significant interaction between the two [ $F(24,222) = 0.853$ ,  $P = 0.666$ ].

##### 3.1.3. Avoidance response on the challenge test

Figure 1(D and E) shows the mean percentage of CS1 and CS2 avoidance responses on the last retraining (drug-free) day and the QUE challenge day. On the retraining day, rats in different groups all had a higher level of avoidance responding to the CS1 than to



**Figure 2.** Effect of repeated subcutaneous administration of quetiapine (5, 15, 25 and 50 mg/kg, s.c., -60 min) on CS1 – (A) and CS2 (B) – elicited avoidance response, escape response (C) during the 7 drug test days, and its effect on the CS1 – (D) and CS2 – (E) avoidance response on the quetiapine challenge day (quetiapine 15 mg/kg, s.c.) in nicotine and phencyclidine pretreated rats. Percentages of avoidance or escape response (mean+S.E.M.) made by nicotine and phencyclidine pretreated rats in the 5 groups on the last training day and during the 7 drug test days, on the last retraining (drug-free) day and the quetiapine challenge day are shown. \* $P < 0.05$  in comparison to the vehicle group.

the CS2, and there was no significant group difference. A split-plot ANOVA showed a main effect of CS condition [ $F(1,37) = 68.300$ ,  $P < 0.001$ ], but no main effect of group [ $F(4,37) = 1.387$ ,  $P = 0.257$ ], nor a CS condition  $\times$  group interaction [ $F(4,37) = 1.421$ ,  $P = 0.246$ ]. On the challenge day, rats previously treated with various doses of QUE for 7 days did not differ from those previously treated with vehicle in both CS1 and CS2 avoidance. Two-way ANOVA showed a main effect of CS condition [ $F(1,37) = 135.491$ ,  $P < 0.001$ ], but no main effect of group [ $F(4,37) = 0.866$ ,  $P = 0.494$ ], nor CS condition  $\times$  group interaction [ $F(4,37) = 1.086$ ,  $P = 0.378$ ].

### 3.2. Experiment 2: Effect of repeated subcutaneous administration of QUE on CS1 and CS2 avoidance in nicotine and PCP pretreated rats

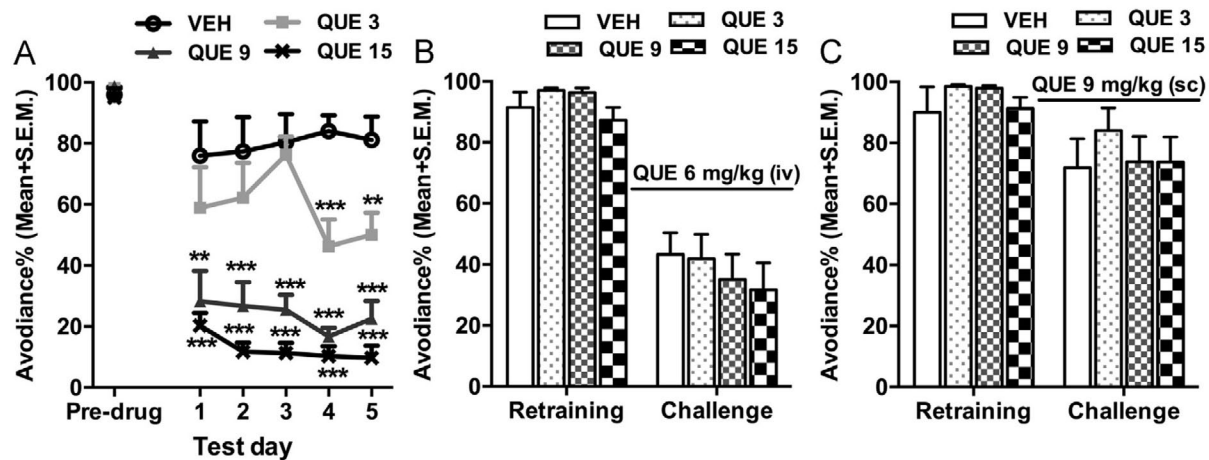
#### 3.2.1. Avoidance response during the drug treatment days

Figure 2(A and B) shows the mean percentage of CS1 avoidance (A) and CS2 avoidance (B) on the last training (pre-drug) day and during the 7 drug test days. There was no significant group difference on the pre-drug day [ $F(4,37) = 0.446$ ,  $P = 0.774$ ]. Throughout the QUE test phase, only the QUE 50 group displayed significantly lower percentages of CS1 and CS2 avoidance, especially towards the end of the drug test phase. A split-plot ANOVA indicated a main effect of group [ $F(4,29) = 4.520$ ,  $P = 0.006$ ], a main effect of CS condition [ $F(1,29) = 180.803$ ,  $P < 0.001$ ], and a significant day

$\times$  group interaction [ $F(24,174) = 1.812$ ,  $P = 0.016$ ]. There was no main effect of day [ $F(6,174) = 1.460$ ,  $P = 0.195$ ], nor any other interactions (all  $ps > 0.217$ ). Post-hoc Fisher's LSD tests showed the QUE 50 group was significantly different from all other groups (all  $p < 0.023$ ). One-way ANOVAs followed by post-hoc Fisher's LSD tests on each test day revealed that the QUE 50 group had significantly lower CS1 avoidance than the VEH group and other QUE groups on the last 3 test days, all  $P < 0.016$ , and significantly lower CS2 avoidance on days 3–5 and day 7, all  $P < 0.05$ .

#### 3.2.2. Escape response during the drug treatment days

Figure 2C shows the mean percentage of escape response on the last training (pre-drug) day and during the 7 drug test days. There was no significant group difference on the pre-drug day [ $F(4,29) = 0.257$ ,  $P = 0.903$ ]. In the QUE test phase, a split-plot ANOVA indicated a main effect of group [ $F(4,29) = 3.647$ ,  $P = 0.016$ ], but no main effect of day [ $F(6,174) = 1.226$ ,  $P = 0.295$ ], nor a day  $\times$  group interaction [ $F(24,174) = 1.216$ ,  $P = 0.234$ ]. Post-hoc Fisher's LSD tests showed that the QUE 50 group had significantly higher escape percentages than the vehicle group ( $P = 0.015$ ). It also had significantly higher escape percentages than the other QUE groups (all  $P < 0.021$ ) except the QUE 15 group ( $P = 0.153$ ). One-way ANOVAs followed by post-hoc Fisher's LSD tests on each test day revealed that the QUE 50 group had significantly more escapes than the VEH group on the last 3 test days, all  $P < 0.013$ , higher than the



**Figure 3.** Effect of repeated intravenous administration of quetiapine (3, 9 and 15 mg/kg, i.v., –20 min) on conditioned avoidance response during the 5 drug test days (A) and the 2 drug challenge days (B: quetiapine 6 mg/kg, i.v.; C: quetiapine 9 mg/kg, s.c.). Percentages of avoidance (mean+S.E.M.) made by normal rats in the 4 groups on the last training day (pre-drug) and during the 5 drug test days, on the last retraining (drug-free) day and the quetiapine challenge day are shown. \*\* $P < 0.01$ , \*\*\* $P < 0.001$  in comparison to the vehicle group.

QUE 25 group on all days except day 1 and day 4, all  $P < 0.008$ , and higher than the QUE 5 group on days 2–3 and day 5, all  $P < 0.026$ .

### 3.2.3. Avoidance response on the challenge test

Figure 2(D and E) shows the mean percentage of CS1 and CS2 avoidance responses on the last retraining (drug-free) day and the QUE challenge day. Before the QUE challenge, rats showed significantly higher CS1 avoidance relative to CS2 avoidance, but there was no significant group difference. There was a main effect of CS condition [ $F(1,29) = 55.272$ ,  $P < 0.001$ ], but no main effect of group [ $F(4,29) = 1.100$ ,  $P = 0.375$ ], nor significant CS condition  $\times$  group interaction [ $F(4,29) = 1.652$ ,  $P = 0.188$ ]. On the challenge test, the group differences were not apparent. A split-plot ANOVA showed a main effect of CS condition [ $F(1,29) = 56.247$ ,  $P < 0.001$ ], but no main effect of group [ $F(4,29) = 1.241$ ,  $P = 0.316$ ], nor a significant CS condition  $\times$  group interaction [ $F(4,29) = 1.023$ ,  $P = 0.412$ ].

### 3.3. Experiment 3: Effect of repeated intravenous administration of QUE treatments on conditioned avoidance in normal rats

#### 3.3.1. Avoidance response during the drug treatment days

Figure 3A shows the mean percentage of avoidance responses on the last training (pre-drug) day and throughout the 5 drug test days. On the pre-drug day, there was no significant group difference [ $F(3,32) = 0.589$ ,  $P = 0.627$ ]. Throughout the QUE test phase, QUE 9.0 and 15.0 mg/kg (i.v.) caused a strong suppression of avoidance responding. A split-plot ANOVA revealed a main effect of group [ $F(3,32) = 30.367$ ,  $P < 0.001$ ], but no main effect of day [ $F(4,128) = 1.687$ ,  $P = 0.157$ ], nor any significant interaction between the two [ $F(12,128) = 1.408$ ,  $P = 0.170$ ]. Post-hoc LSD tests showed that all 3 QUE groups had significantly lower avoidance than the VEH group (QUE 3.0,  $P = 0.013$ ; QUE 9.0 and 15.0, both  $P < 0.001$ ). QUE 9.0 and 15.0 groups also had significantly lower avoidance than the QUE 3.0 group (both  $P < 0.001$ ). One-way ANOVA on each test day revealed that the QUE 9.0 and 15.0 groups had significantly lower avoidance than the VEH group on all 5 days (all  $P < 0.004$ ), while the QUE 3.0 group showed lower avoidance than the VEH group only on days 4 and 5 ( $P < 0.001$ ). Additionally, QUE 9.0 and 15.0 groups have lower avoidance than the QUE 3.0 groups on all 5 days (all  $P < 0.045$ ). These findings indicate that QUE was able to dose-dependently cause a persistent suppression of the avoidance response across the drug test sessions.

#### 3.3.2. Avoidance response on the challenge test

Figure 3B shows the mean percentage of avoidance responses on the 1st retraining day and the 1st QUE challenge day (6.0 mg/kg, i.v.). No significant group difference was found [the 1st pre-drug day,  $F(3,32) = 1.716$ ,  $P = 0.183$ ; the 1st challenge day,  $F(3,32) = 0.477$ ,  $P = 0.700$ ].

After 2 days of retraining, all rats were challenged again with QUE (9.0 mg/kg, s.c.). As shown in Figure 3C, none of the groups differed from each other on the 2nd retraining day [ $F(3,32) = 0.880$ ,  $P = 0.462$ ] or on the 2nd challenge day [ $F(3,32) = 0.434$ ,  $P = 0.730$ ], indicating no long-term alteration of behavioral sensitivity to QUE after repeated intravenous QUE treatment.

## 4. Discussion

Using heterogeneous groups of rats (i.e. drug-naïve and nicotine and/or PCP treated rats), two CAR test procedures (CS1+CS2 vs. CS1-only) and two drug administration routes (s.c. vs. i.v.), we demonstrated that under the subcutaneous administration condition, only the high-dose of QUE (50 mg/kg) was able to cause a persistent and comparable suppression of avoidance responses to both CS1 and CS2 during the repeated drug treatment phase (Experiments 1 and 2; Figure 1 and Figure 2). However, under the intravenous administration condition, all 3 doses of QUE (3.0, 9.0 and 15.0 mg/kg) exhibited this effect (Experiment 3; Figure 3). In the challenge tests when all rats were injected with QUE, those who had been treated with QUE previously did not make more or fewer avoidance responses than those who had been treated with vehicle. This result was consistent across the 3 experiments, suggesting that prior QUE experience or treatment history did not cause a long-term change in the behavioral sensitivity to QUE, regardless of the route of drug administration. Thus, under the current test conditions, QUE does not appear to show a clozapine-like tolerance effect (Feng et al., 2013b, Li et al., 2012, Li et al., 2010 and Qiao et al., 2013), nor does it show an olanzapine-like sensitization effect (Li et al., 2009b, Li et al., 2010 and Swalve and Li, 2012), although they all belong to the same atypical antipsychotic drug group.

As mentioned in Section 1, QUE's avoidance disruptive effect has been demonstrated before (Bjorkholm et al., 2013 and Wadenberg et al., 2001). Wadenberg et al. (2001) examined the relation between striatal dopamine  $D_2$  occupancy and efficacy of avoidance suppression. They found that QUE at 5, 10, 25, 50, 75 and 100 mg/kg gave rise to a dose-dependent increase in striatal dopamine



D<sub>2</sub> occupancy in rats (58–81%) at the 1 h time point after injection. In the avoidance test, they found that QUE at 20 or 40 mg/kg suppressed avoidance responding 20 min after injection. QUE at 40 mg/kg maintained its suppression even 90 min after administration. Bjorkholm et al. (2013) used an intravenous drug administration route and found that QUE at 6 and 9 mg/kg (i.v.) produced a relatively transient suppression of avoidance 5 min after injection, but not after 30 min. In the present study, we also showed that QUE at 9.0 and 15.0 mg/kg administered intravenously disrupted avoidance responding at 20 min post injection and this effect persisted throughout the 5-day testing period (Experiment 3). One methodological difference between Bjorkholm et al. (2013) and Experiment 3 was that we tested rats under the CS-only condition, while Bjorkholm et al. (2013) tested them under the CS-US (shock) condition. This difference might explain why we observed such a robust and severe suppression (reduced to ~20% avoidance level), while Bjorkholm et al. (2013) only observed a mild suppression (reduced to ~50% level).

In comparison to other atypical antipsychotic drugs, such as olanzapine, risperidone and clozapine, QUE displays a relatively weak and short duration of action on avoidance responding. One obvious reason is that QUE has a faster dissociation rate from dopamine D<sub>2</sub> receptors and does not cause a sustained higher D<sub>2</sub> occupancy (>80%) than other atypical drugs (Kapur and Seeman, 2000). The QUE 50 mg/kg (s.c.) tested in the present study only produces 74% D<sub>2</sub> occupancy (Wadenberg et al., 2001). Given that D<sub>2</sub> blockade is critical for antipsychotic action (Seeman, 2002) and action in the CAR model (Wadenberg et al., 2001), it could be said that QUE transiently disrupts avoidance behavior because it only transiently blocks dopamine D<sub>2</sub> receptors. The second possible reason is that QUE does not produce norquetiapine in rodents (Bjorkholm et al., 2013). Because norquetiapine has a potent inhibitory action against the norepinephrine transporter (NET) (Jensen et al., 2008), and the NET inhibition by reboxetine (a selective NET inhibitor) often enhances the avoidance-disruptive effect of QUE (Bjorkholm et al., 2013), it is reasonable to suggest that norquetiapine could potentially enhance the avoidance-disruptive effect of QUE. Therefore, lack of this metabolite in rats may contribute to the overall weak effect of QUE.

In our previous studies of the motivational salience attenuation action of antipsychotics, we have shown that atypical antipsychotics (e.g. clozapine, olanzapine and risperidone) suppress avoidance responses elicited by a less salient conditioned stimulus (e.g. pure tone CS2 as it was only partially reinforced) to a greater extent than avoidances elicited by a more salient stimulus (e.g. white noise CS1 as it was reinforced in every trial), regardless of the baseline difference in the number of CS1 and CS2 avoidances (Li et al., 2009b, 2012; Zhang et al., 2011). The differential sensitivity to QUE (50 mg/kg) of CS1 and CS2 avoidance was not apparent in our current experimental condition, although we did observe that prior conditioning to CS1 renders CS2 less effective in eliciting an avoidance response (Figure 1 and Figure 2). Why QUE did not show a preferential suppression of CS2 avoidance over CS1 avoidance is not entirely clear. Besides QUE's relative weaker effect on avoidance than other atypicals, the procedural differences between the present study and previous ones could be a factor. In the previous studies, rats were trained in the CS1 and CS2 avoidance conditioning procedure first, and then tested in the same procedure; while in the present study, rats were first trained in the CS1 avoidance and then tested in the mixed CS1 and CS2 avoidance procedure. This issue will be further examined in the future study to directly compare QUE with other atypical antipsychotics in the same test procedure.

As mentioned before, our recent work on the long-term effects of repeated antipsychotic treatment has revealed two basic

behavioral patterns: *sensitization* and *tolerance* in the CAR model and also in the phencyclidine-induced hyperlocomotion model (Feng et al., 2013b, Gao and Li, 2013, Li et al., 2012, Mead and Li, 2010, Qiao et al., 2013, Swalve and Li, 2012 and Zhang and Li, 2012). Specifically, we show that repeated administration of haloperidol, olanzapine or risperidone daily for 5–7 days tends to cause a progressively increased inhibition of avoidance responding. When rats are given a challenge dose of these drugs at a later point, they often make significantly *fewer* avoidance responses than those that are treated with these drugs for the first time (Li et al., 2009b, Li et al., 2010, Mead and Li, 2010, Qiao et al., 2013, Swalve and Li, 2012 and Zhang and Li, 2012). Clozapine, on the other hand, displays an opposite behavioral pattern (tolerance). During the daily drug test phase, repeated administration of clozapine causes no apparent sensitization or tolerance. But on the challenge test, rats previously treated with clozapine make significantly *more* avoidance responses than those that are treated with clozapine for the first time (Feng et al., 2013b, Li et al., 2010 and Qiao et al., 2013). QUE, very much like clozapine, has high to moderate affinities for  $\alpha_1$ -adrenergic, 5-HT<sub>2A</sub>, H<sub>1</sub> and low affinities for D<sub>1</sub>, D<sub>2</sub> and  $\alpha_2$ -adrenergic receptors (Jibson and Tandon, 1998; Miyamoto et al., 2005), and fast dissociation from the D<sub>2</sub> receptor (Kapur and Seeman, 2000; Kapur et al., 2000). We thus hypothesized that repeated treatment of QUE would cause a clozapine-like tolerance effect in the CAR model. Results indicate that although there was a trend for QUE tolerance, i.e. rats previously treated with QUE had higher avoidance than those previously treated with vehicle, the difference failed to reach a significant level based on the one-way ANOVA. Therefore, if QUE does cause a clozapine-like tolerance effect, this effect may still be relatively weak. Because antipsychotic sensitization and tolerance are modulated by various experimental parameters (e.g. drug doses, number of drug administrations, test-retest intervals, etc.), more studies are needed to further determine the features of QUE repeated treatment effect.

The clinical efficacy of QUE is similar to those of other atypical antipsychotic drugs. Its mechanism of action is also relatively similar. Like other atypical drugs, the antipsychotic efficacy of QUE in schizophrenia is thought to be mediated by its transient high D<sub>2</sub> blockade in the striatum (Kapur et al., 2000) or a combination of dopamine D<sub>2</sub> and serotonin 5-HT<sub>2</sub> antagonisms in the cortical and subcortical areas (Ichikawa et al., 2002). Even though both clozapine and QUE are well tolerated by the patients, they have different pharmacokinetics. For example, the elimination half-life of QUE (approximately 6 h) is shorter than that of clozapine (more than 10.2 h), and its active metabolites, e.g. norclozapine (10.2 h) (Fang and Mosier, 2014; Guitton et al., 1999; Winter et al., 2008). Therefore, although the present study did not find strong evidence at the behavioral level linking QUE with other atypicals, especially clozapine, its behavioral similarities with other atypicals should not be dismissed. Indeed, in the phencyclidine-induced prepulse inhibition (PPI) of acoustic startle reflex test (Li et al., 2011), we found that repeated administration of both QUE and clozapine similarly maintained their improvement effect on phencyclidine-induced PPI deficits. Future work directly comparing QUE with other atypicals in the CAR model as well as other behavioral tests of antipsychotic activity (e.g. phencyclidine-induced hyperlocomotion model) may be able to reveal the behavioral mechanisms of action of QUE and its possible similarities and differences to other drugs. Overall, the present findings suggest that quetiapine is capable of suppressing avoidance response and maintains its suppression over the treatment period, a profile shared by other atypical antipsychotic drugs. However, prior quetiapine treatment does not cause a long-term change in drug sensitivity (i.e. sensitization or tolerance), a peculiar feature deserving further investigation.

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