European Journal of Pharmacology 769 (2015) 154–161

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Behavioural pharmacology

Effects of repeated quetiapine treatment on conditioned avoidance responding in rats

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ARTICLE INFO

Article history:
Received 11 May 2015
Received in revised form
5 November 2015
Accepted 5 November 2015
Available online 14 November 2015

Keywords:
Quetiapine
CS1 and CS2
Conditioned avoidance response
Sensitization
Tolerance

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.

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., 2004, 2007, 2009a, 2009b, 2012, 2010; 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

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http://dx.doi.org/10.1016/j.ejphar.2015.11.011
0014-2999/

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 D2 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-naive 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-naive Sprague-Dawley rats (226–250 g upon arrival) were used. Rats were housed two per cage, in transparent polycarbonate cages ($48.3 \times 26.7 \times 20.3$ 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; 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; 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