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Long-term impacts of adolescent risperidone treatment on behavioral responsiveness to olanzapine and clozapine in adulthood

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ABSTRACT

This preclinical study investigated how a short-term risperidone treatment in adolescence impacts antipsychotic response to olanzapine and clozapine in adulthood. Antipsychotic effect was indexed by a drug's suppressive effect on avoidance responding in a rat conditioned avoidance response (CAR) model. Male adolescent Sprague–Dawley rats were first treated with risperidone (1.0 mg/kg, sc) or sterile water and tested in the CAR model for 5 consecutive days from postnatal days P 40 to 44. After they became adults (~P 80–84), they were switched to olanzapine (0.5 mg/kg, sc), clozapine (5.0 mg/kg, sc) or vehicle treatment and tested for avoidance for 5 days. During the adolescent period, repeated risperidone treatment produced a persistent inhibition of avoidance response. Throughout the 5 days of adulthood drug testing, rats previously treated with risperidone in adolescence made significantly fewer avoidance responses than the vehicle ones when they all were switched to olanzapine, indicating a risperidone-induced enhancement of behavioral sensitivity to olanzapine. In contrast, when switched to clozapine, rats previously treated with risperidone made significantly more avoidance responses than the vehicle rats, indicating a risperidone-induced decrease of behavioral sensitivity to clozapine. Performance in the prepulse inhibition of acoustic startle response in adulthood was not altered by adolescent risperidone treatment. Collectively, adolescent risperidone exposure induced a long-term change in behavioral sensitivity to other atypical antipsychotic drugs, with the specific direction of change (i.e., increase or decrease) dependent on the drug to be switched to. These long-lasting changes are likely mediated by drug-induced neuroplastic changes and may also have significant clinical implications for antipsychotic treatment of chronic patients with an early onset of psychotic symptoms.

1. Introduction

Adolescence (human: 10–19 years old; rats: 35–60 days old) (Andersen et al., 2000) is a period in which the brain and various psychological functions undergo dramatic transitions. It is also the time when symptoms of a variety of severe mental disorders often manifest. Accumulating evidence indicates that adolescents may have enhanced sensitivity to psychotropic drugs (Findling et al., 2010; Kumra et al., 2008; Sikich et al., 2008), and pharmacological interventions during this period alter brain structure and function in ways that are detectable at multiple levels (Singh and Chang, 2012). Such alterations are often long-lasting and could alter the trajectory of the brain and behavioral development of pediatric patients, which in turn may change their later response to drug treatment as adults. As pediatric treatment is administered at a critical period of rapid brain and behavioral development, there is a crucial need to evaluate the possible long-term impacts of antipsychotic medications in adolescence on psychological functions and drug response, and to identify the neurobiological mechanisms.

In recent years, we have focused our attention on the issue of how early antipsychotic exposure in adolescence modifies later behavioral responsiveness to antipsychotic re-exposure in adulthood (Qiao et al., 2013). We have used the conditioned avoidance response (CAR) model, a validated animal test of antipsychotic activity (Wadenberg and Hicks, 1999), to examine this issue. The general approach follows our adult CAR work which involves two phases of drug effect assessment: an induction phase and an expression phase (Feng et al., 2013; Li et al., 2010, 2012b; Mead and Li, 2010; Swalve and Li, 2012; Zhang and Li, 2012). In the induction phase, rats are repeatedly treated

Abbreviations: BrdU, 5′-Bromo-2-deoxyuridine; CAR, conditioned avoidance response; CLZ, clozapine; CLZ 5.0, clozapine 5.0 mg/kg; CS, conditioned stimulus; DA, dopamine; FDA, Food and Drug Administration; GABA, gamma amino butyric acid; OLZ, olanzapine; OLZ 0.5, olanzapine 0.5 mg/kg; P, postnatal; PCP, phencyclidine; PFC, prefrontal cortex; PPI, prepulse inhibition; sc, subcutaneously; RIS, risperidone; RIS 1.0, risperidone 1.0 mg/kg; VEH, vehicle; US, unconditioned stimulus; % PPI, percent prepulse inhibition.

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with an antipsychotic drug or vehicle for a certain number of days (e.g., 5 or 7 days), and the drug's suppressive effect on avoidance response is recorded daily. In the expression phase, all rats are given a challenge dose of the drug and tested for avoidance response. This paradigm allows us to reveal that antipsychotic efficacy (as indexed by a drug's suppressive effect on avoidance response) can be increased or decreased with only 5 days of repeated drug treatment in adolescence. Specifically, we found that adolescent olanzapine treatment makes animals more sensitive to olanzapine re-exposure when they become adults (termed olanzapine sensitization), whereas clozapine treatment in adolescence makes animals less sensitive to clozapine re-exposure in adulthood (termed clozapine tolerance) (Qiao et al., 2013). These findings have been validated in the PCP-induced hyperlocomotion model (Shu et al., accepted for publication) — another behavioral test of antipsychotic activity (Millan et al., 1999; Sun et al., 2009).

In our adult rat studies, we have also observed a cross-sensitization between haloperidol and olanzapine (Li et al., 2007; Mead and Li, 2010). Specifically, rats that had been treated with haloperidol showed enhanced sensitivity to the avoidance disruptive effect of olanzapine in a drug challenge test, and vice versa. A cross-sensitization was also found from risperidone to olanzapine, as rats previously treated with risperidone (1.0 mg/kg) showed stronger reactivity to the avoidance-disruptive effect of olanzapine (Zhang et al., 2011). Recently, we further demonstrated a cross-sensitization from asenapine to olanzapine (Qin et al., 2013). These findings, together with many from drug discrimination studies (Porter and Prus, 2009), suggest that there is a common mechanism underlying sensitization effects induced by various antipsychotics despite their different chemical structures and receptor binding profiles.

If cross-sensitization is a general principle associated with antipsychotic sensitization, one would expect to ascertain it in adult rats that have experienced an antipsychotic drug earlier when they were adolescents. The present study reports our investigation of the possible cross-sensitization from risperidone to olanzapine and clozapine in the CAR model from adolescence to adulthood. Risperidone is an antipsychotic agent with a benzisoxazole chemical structure that has potent dopamine D_2, serotonin 5-HT_{2A}, and α_1 receptor antagonism (Miyamoto et al., 2005). It is a Food and Drug Administration (FDA)-approved antipsychotic drug for pediatric use and has been one of the most prescribed antipsychotic agents for children and adolescents (Patel et al., 2005). Thus, the present study not only is important for the purpose of examining the general principles of antipsychotic sensitization and cross-sensitization, but also has significant clinical implications, as drug switching is quite common in people with schizophrenia during the course of optimizing therapeutic regimens for individual patients (Rosenheck et al., 2009). In addition, we also assessed whether adolescent risperidone treatment would cause a long-lasting impairment on instrumental learning in a modified avoidance conditioning task in adulthood or an attention deficit in a prepulse inhibition test (Swerdlow et al., 2000).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley adolescent rats from Charles River Inc. (Portage, MI) (postnatal days, P 22–26, average age was assumed at P 24, 51–75 g on delivery date) were used. After arrival, they were housed two per cage, in 48.3 cm × 26.7 cm × 20.3 cm transparent polycarbonate cages under 12-h light/dark conditions (light on between 6:30 am and 6:30 pm). 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 5 days of habituation to the animal facility before being used in the experiments. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska-Lincoln.

2.2. Drugs

Risperidone (RIS), olanzapine (OLZ), and clozapine (CLZ) (gifts from the NIMH drug supply program) were dissolved in distilled sterile water with 0.5–1.0% glacial acetic acid. They were administrated subcutaneously (sc) at 1.0 ml/kg. We tested RIS at 1.0 mg/kg during the adolescent period because our preliminary study shows that this dose of RIS induces a long-term sensitization effect that persists into adulthood (unpublished observation). Also in adult rats, RIS at 1.0 mg/kg disrupts avoidance response and other fear responses (Sun et al., 2010; Zhang et al., 2011), and gives rise to a clinically comparable level of striatal D2 occupancy (65–80%)(Kapur et al., 2003). OLZ at 0.5 mg/kg and CLZ at 5.0 mg/kg are commonly used challenge doses in the study of antipsychotic sensitization and tolerance (Feng et al., 2013; Li et al., 2012b; Qiao et al., 2013; Swalve and Li, 2012; Zhang and Li, 2012).

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, 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). The conditioned stimuli (either a 76 dB white noise CS1 or an 85 dB 2800 Hz pure tone CS2) were produced by a speaker mounted on the ceiling of the cubicle, centered above the shuttle box. Illumination was provided by two houselights mounted at the top of each compartment. 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. Prepulse inhibition of acoustic startle reflex apparatus

The prepulse inhibition (PPI) test was performed using six Startle Monitor Systems (Kinder Scientific, Julian, CA). Each system, controlled by a PC, was housed in a compact sound attenuation cabinet (36 cm wide × 28 cm deep × 50 cm high). A speaker (diameter: 11 cm) mounted on the cabinet's ceiling was used to generate acoustic stimuli (70 dB–120 dB). The startle response was measured by a piezoelectric sensing platform on the floor, which was calibrated daily. During testing, a rat remained in a rectangular box made of transparent Plexiglas (19 cm wide × 9.8 cm deep × 14.6 high) with an adjustable ceiling positioned atop the box, providing only limited restraint while prohibiting ambulation.

2.5. Experimental procedure

This experiment consisted of the following four stages: repeated risperidone testing in adolescence; avoidance retraining/testing in adulthood; drug switching to olanzapine or clozapine in adulthood; and PPI assessment. Fig. 1 details the timeline of events and group information.