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Neonatal quinpirole treatment produces prepulse inhibition deficits in adult male and female rats

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ABSTRACT

We have shown that repeated neonatal quinpirole (QUIN; a dopamine D2-like receptor agonist) treatment in rats produces long-lasting supersensitization of dopamine D2 receptors that persists into adulthood but without producing a change in receptor number. The current study was designed to analyze the effects of neonatal QUIN on auditory sensorimotor gating as measured through prepulse inhibition (PPI). Male and female Sprague–Dawley rats were neonatally treated with QUIN (1 mg/kg) or saline from postnatal days (P)1–21. At P60, the number of yawns was recorded for a 1 h period in response to an acute QUIN (1 mg/kg) injection as yawning is a D2-like receptor mediated behavioral event. Five days later, rats began (PPI) behavioral testing in two phases. In phase I, three different prepulse intensities (73, 76, and 82 dB) were administered 100-ms before a 115 dB pulse on 10 consecutive days. In phase II, three different interstimulus intervals (ISI; 50, 100, and 150 ms) were inserted between the 73 or 76 dB prepulse and 115 dB pulse over 10 consecutive days of testing. A PPI probe trial was administered at the end of each phase after an acute 100 μg/kg i.p. injection of QUIN to all animals. Replicating previous work, neonatal QUIN enhanced yawning compared to controls, verifying D2 receptor supersensitization. Regarding PPI, neonatal QUIN resulted in deficits across both phases of testing persistent across all testing days. Probe trial results revealed that acute QUIN treatment resulted in more robust PPI deficits in neonatal QUIN animals, although this deficit was related to prepulse intensity and ISI. These findings provide evidence that neonatal QUIN treatment results in deficits of auditory sensorimotor gating in adulthood as measured through PPI.

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1. Introduction

Prepulse inhibition (PPI) measures sensorimotor gating and is disrupted in patients with disorders involving the mesocortical dopamine pathways, such as schizophrenia, Huntington's disease, obsessive compulsive disorder (OCD), and Tourette's syndrome (Braff et al., 1995; Hoenig et al., 2005; Swerdlow, 2013; Swerdlow et al., 1995, 2006). To model these disruptions in rats, PPI has typically been measured after manipulation of dopamine pathways with various drug treatments. For example, repeated administration or intra-accumbal infusion with quinpirole (QUIN), a dopamine D2-like receptor agonist results in PPI deficits in rats (Wan and Swerdlow, 1993). Likewise, antipsychotic drugs, which all block the D2 receptor with some affinity, have been shown to alleviate PPI deficits produced by stimulation of dopamine brain pathways using rodent models (Kapur and Mamo, 2003; Kumari and Sharma, 2002). These findings suggest that changes in D2 receptor activity affects sensorimotor gating as is tested by PPI.

Past studies from our laboratory have shown that neonatal treatment of rats with QUIN during the first 3–4 weeks of life results in an increase of D2-like receptor sensitivity that persists throughout the animal's lifetime without producing a change in D2 receptor number (Kostrzewa, 1995). We have found a number of behavioral, neurobiological and genetic consistencies of this model with schizophrenia (Brown et al., 2012). One particularly important finding using this model revealed that cognitive deficits and decreases in neurotrophic factor protein produced by neonatal QUIN treatment were alleviated by treatment with olanzapine, an atypical antipsychotic (Thacker et al., 2006), also consistent with findings in schizophrenics (Cuesta et al., 2009; Durany et al., 2001; Gama et al., 2007; Hammonds and Shim, 2009; Kurosawa et al., 2007). A critical finding in any rodent model of disease is that a common treatment for that disease is also found to be effective in the model. However, PPI, a behavioral hallmark characteristic of schizophrenia, has yet to be evaluated in the neonatal QUIN model. The present study tested the hypothesis that persistent D2 receptor supersensitivity as is produced by repeated neonatal treatment with quinpirole will result in PPI deficits in these same rats tested as adults.

In addition, sex differences in PPI will be analyzed because sex differences have been observed in humans and rats after D2 receptor

Abbreviations: PPI, prepulse inhibition; ISI, interstimulus interval; QUIN, quinpirole; NAc, nucleus accumbens.

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sensitivity (Kaasinen et al., 2001; Pohjalainen et al., 1998; Schindler and Carmona, 2002). In addition, male rats have an increase of dopamine D1 and D2 receptor ligand binding during adolescence in the nucleus accumbens (NAc) and striatum as compared to females, which could also influence later dopamine development (Andersen et al., 1997; Andersen and Teicher, 2000). Additionally, in humans, females have decreased PPI performance as compared to males (Abel et al., 1998; Q. Rahman et al., 2003; Swerdlow et al., 1993), which has been replicated in rats but this effect is strain-dependent (Faraday, 2002). Interestingly, females do have fluctuations of PPI performance across the menstrual cycle, perhaps increasing variability leading to reductions in PPI as compared to males (Swerdlow et al., 1997). Presumably, the basis of these sex differences is due to the estrogen system's strong influence on the mesoaccumbal dopamine system and therefore also affecting PPI (Becker, 1999; Becker et al., 1982; Becker and Rudick, 1999; Di Paolo et al., 1988; Joyce and Van Hartesveldt, 1984a,b).

In the current study, we tested whether PPI deficits existed in neonatal QUIN rats using two phases of testing. In Phase I, we used a relatively standard auditory sensorimotor gating protocol, with 73, 76, and 82 dB prepulse intensities. However, we tested over 10 days, using a PPI behavioral protocol similar to that of previous studies (Berger et al., 2011; Culm and Hammer, 2004,). The rationale for using a multiple day testing protocol was to analyze whether PPI may change over time in rats neonatally treated with QUIN and whether it may improve towards control levels. In Phase II, we manipulated the interstimulus interval (ISI) to investigate whether changing this task parameter may alleviate or improve PPI performance in neonatal QUIN animals. For example, increasing the ISI between the prepulse and pulse has been shown to improve PPI performance after ketamine administration (Mansbach and Geyer, 1991) as well as after intrahippocampal infusions of the nonstructural protein Tat (Fitting et al., 2006). Finally, after each phase of testing, we investigated whether acute QUIN treatment would change PPI performance. Previous data has shown that adult acute QUIN administration to animals that were also neonatally treated with QUIN results in decreases of dorsal striatal dopamine release, presumably due to its activation of the sensitized presynaptically located inhibitory D2 autoreceptors (Nowak et al., 2001). Presumably, a decrease of dopamine release as is produced by acute QUIN treatment may result in improved PPI performance in animals with supersensitized D2 receptors.

2. Material and methods

2.1. Subjects

A total of four adult male and eight adult female adult rats were purchased from Harlan, Inc. (Indianapolis, IN). Upon arrival, each female rat was housed separately in a plastic polycarbonate cage with a male rat for approximately 14 days and then separated. The day of birth was counted as postnatal day (P)0. The offspring of each breeding pair were used as subjects in this study. All animals were weaned from the female dam at P21, socially housed, and behaviorally tested as adults beginning at P60. Only one male and female from each litter were utilized per drug condition, and there were a total of eight males and six females in each of the four conditions, for a total of 28 animals that were behaviorally tested. Animals were housed in an AAALAC-accredited climate-controlled animal colony with a 12-hour on/off light/dark cycle, and all testing was performed during the light portion of the cycle. All procedures in this study were approved by the University Committee on Animal Care at East Tennessee State University that is in compliance with the NIH Guide on Care and Use in Animals.

2.2. Drugs

Quinpirole HCl (Sigma-Aldrich, St. Louis, MO) (1 mg/kg) and 0.9% saline vehicle were used in the current study.

2.3. PPI behavioral apparatus

The startle testing was performed in ventilated, SR-lab sound-attenuated chambers (San Diego Instruments, San Diego, CA, USA). Rats were placed in cylindrical Plexiglas chambers that were 10 cm in diameter and mounted on a platform inside this chamber located 25 cm below a high-frequency loudspeaker. A 70 dB white noise provided the background auditory stimulus. The animal was placed within the cylinder for testing, and Plexiglas walls kept the animal within the cylinder during testing. The animal was not restrained in these cylinders, rather, the animal was able to move and turn around within this enclosure. The startle response of the animal was measured through a unit mounted underneath the Plexiglas cylinder that sent an analog signal to the computer that was digitized and stored in the computer. Calibrations were performed before behavioral testing commenced to maintain accurate acoustic stimuli presentations and mechanical-vibration measures.

2.4. Behavioral procedures

2.4.1. Neonatal drug treatment and yawning test

Beginning on P1, rats received once daily intraperitoneal (i.p.) injections of either quinpirole HCl (1 mg/kg) or saline for the next 21 consecutive days (P1–21). Injection volumes were kept equivalent for all animals within each drug condition. We have previously used this dose and treatment regimen and observed increases in D2 supersensitivity as validated by increased yawning in response to quinpirole (Brown et al., 2012; Kostrzewa, 1995) as well as decreased expression of regulators of G-protein signaling 9 (RGS9) expression in the frontal cortex, dorsal striatum, and nucleus accumbens (Maple et al., 2007). RGS9 has been shown to be important in regulating D2 receptor signaling (Z. Rahman et al., 2003) In the present study, we verified increased D2 receptor sensitivity through a single injection of quinpirole (1 mg/kg, i.p.), and yawning behavior was observed for 1 h. Yawning has been shown to be a D2-like receptor mediated behavioral event (Cooper et al., 1989; Yamada et al., 1986). Two observers recorded the number of yawns for each rat and were blind to the condition. During this test, rats were singly placed in a cage without bedding, because we have observed that the animals will often gnaw on the bedding and this will supersede yawning.

2.4.2. Phase I: PPI utilizing a 100-ms ISI and three auditory intensities of the prepulse

Approximately five days after verification of increased D2 receptor sensitivity via the yawning test, animals began PPI testing on P65. On the first day of testing, animals were acclimated to the chamber alone and cylindrical enclosure with only white noise presented. The following day, PPI testing began. There were two phases of PPI testing, and the same animals were used across both phases. At the beginning of each trial, all animals were placed into the cylindrical animal enclosure and were exposed to a 70 dB ambient white noise for a 5 min acclimation period. The acclimation period was immediately followed by a test session consisting of the randomized presentation of 32 trials. Of these 32 trials, there were 17 pulse trials and 15 prepulse trials. A *pulse* trial consisted of a high intensity startle auditory stimulus that was 115 dB in auditory intensity and persisted for 40-ms, but no prepulse was given. There were 15 *prepulse* trials that consisted of a prepulse auditory stimulus of 73, 76, or 82 dB (3, 6 or 12 dB above background) intensity that were 20 ms in length given 100 ms before the 40 ms 115 dB pulse. The mean behavioral response after each pulse and prepulse trial was recorded for 100 ms after the stimulus was administered. The average intertrial interval was 15 s. Animals were tested for 10 consecutive days and prepulse and pulse trials were presented in a different random order each day. On the 11th day of testing, a drug challenge of an acute injection of quinpirole (100 μg/kg, i.p.) was administered 15 min prior to PPI testing, see Fig. 1.

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