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Early-life risperidone administration alters maternal–offspring interactions and juvenile play fighting

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ABSTRACT

Risperidone is an antipsychotic drug that is approved for use in childhood psychiatric disorders such as autism. One concern regarding the use of this drug in pediatric populations is that it may interfere with social interactions that serve to nurture brain development. This study used rats to assess the impact of risperidone administration on maternal–offspring interactions and juvenile play fighting between cage mates. Mixed-sex litters received daily subcutaneous injections of vehicle or 1.0 or 3.0 mg/kg of risperidone between postnatal days (PNDs) 14–42. Rats were weaned and housed three per cage on PND 21. In observations made between PNDs 14–17, risperidone significantly suppressed several aspects of maternal–offspring interactions at 1-hour post-injection. At 23 h post-injection, pups administered risperidone had lower activity scores and made fewer non-nursing contacts with their moms. In observations of play-fighting behavior made once a week between PNDs 22–42, risperidone profoundly decreased many forms of social interaction at 1 h post-injection. At 23 h post-injection, rats administered risperidone made more non-social contacts with their cage mates, but engaged in less social grooming. Risperidone administration to rats at ages analogous to early childhood through adolescence in humans produces a pattern of abnormal social interactions across the day that could impact how such interactions influence brain development.

1. Introduction

Over the last decade, antipsychotic drugs (APDs) have been used increasingly to treat a host of psychiatric disorders in children and young adolescents. In 1996, children made up 7% of the total population of APD users—a percentage that doubled by 2005 (Vitiello et al., 2009). The greatest rise in APD prescription rates among different age groups has been for children under the age of 5 (Constantine et al., 2011; Olfson et al., 2012). When used in pediatric populations, over 50% of APD prescriptions target children diagnosed with ADHD, with 20% of prescriptions directed at children with intellectual disabilities and autism (Olfson et al., 2012). The most widely used APD in children is risperidone, with boys receiving a majority of the prescriptions (Domino and Swartz, 2008).

One primary issue regarding APD use, in adults as well as children, is the propensity for APDs to produce sedation (Cohen et al., 2012). In one study (Lemmon et al., 2011) this side effect was identified as the main reason for APD treatment failure in children. This raises a concern that APD-induced sedation could interfere with a number of daily activities in children with psychiatric and neurological disorders. One aspect of daily experience that may be disrupted by APD medication is social interaction between treated children and their parents, siblings, peers, and educators. There is a concern regarding interactions not only when drug blood levels peak, but also during their daily trough. It is possible that, at this latter time point, compensatory behavioral reactions to the absence of drug, as is seen in animals (Muller and Seeman, 1978; Tadokoro et al., 2012), could emerge in children. The impact of APDs on social interaction in children is especially important for two reasons. First, alterations in social interaction during development influence brain maturation and later social competence, as reported in many animal studies (see below). Second, deficits in sociability (e.g., autism) are a symptom of most childhood psychiatric and behavioral disorders treated with APDs.

One indirect, yet informative approach to determining how APDs might affect social interaction is to examine their impact on developing, pro-social mammals. This strategy allows for the analysis of the immediate or delayed effects of APDs on social interaction within a controlled environment and without the intervening factors of brain abnormalities, additional medications, and a host of other factors encountered in clinical settings. The rat may serve as one of the better model systems

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in this regard for three reasons. The effects of APDs on behavior in adult rats are well established (see Bardgett, 2004 for review). The pattern of brain development seen in rats mirrors the trajectory observed in humans (Spear, 2000). Finally, rats demonstrate two well-characterized forms of social behavior during development: maternal–offspring interactions and juvenile play fighting (Cooke and Shukla, 2011; Parent and Meaney, 2008; Pellis et al., 1997; Siviy and Panksepp, 2011).

Early in life, rats depend on their dams for nutrients and warmth, and as they approach the end of the pre-weaning stage of development at postnatal day (PND) 21, begin to investigate their environment more and interact more with their siblings. Much research has focused on the maternal–offspring interactions that occur within the first two weeks of life (see Meaney, 2001 for review), especially maternal licking and grooming. However, dams continue to nurse and carry their pups well into third postnatal week. After weaning, and especially between the onset of puberty and the beginning of adulthood (PNDs 28–45), juvenile rats engage in play-fighting behavior that is marked by agonistic crawl overs and crawl unders, grooming, pouncing, and other social behaviors.

Much research has demonstrated the importance of adequate maternal stimulation during the preweaning period for adult behavior and brain physiology (see Meaney and Szyf, 2005, for review). Likewise, isolation from cage mates and individual variation in play-fighting behavior have been linked to neural and behavioral changes that persist into adulthood (Bell et al., 2010; also see Cooke and Shukla, 2011 for review). If administration of APDs early in life was to disrupt the patterns of maternal–offspring or adolescent social interaction, adult behavioral and brain function may be compromised. To this end, we have recently shown that rats administered risperidone early in life demonstrate locomotor hyperactivity as adults (Bardgett et al., 2013). It has yet to be determined if this change is due to a direct effect of risperidone on the brain or an indirect effect of risperidone on social interaction and other formative experiences during development.

As a means to begin addressing this latter idea, the primary goal of this research was to determine if early-life risperidone administration alters pre- and post-weaning social behaviors in rats. The first purpose of the study was to assess the effects of risperidone on maternal–offspring interactions from PNDs 14–17 at 1 hour and 23 h post-administration. These observation times were chosen to capture the peak drug effects on behavior, and to determine if there are any residual or compensatory effects that emerged when blood drug levels should be at their lowest. Previous studies (Olsen et al., 2008; van Beijsterveldt et al., 1994) have shown that the plasma and brain half-lives of risperidone are approximately 1 and 3.5 h respectively. To confirm the time course of elimination from the plasma after injection, plasma risperidone and its active metabolite, 9-OH-risperidone were measured at 1, 5, and 23 h post-administration. The second purpose of the study was to evaluate the effects of risperidone on play-fighting behaviors observed at 1 hour and 23 h post-administration. Observations were conducted once a week between PNDs 21–42.

2. Materials and methods

2.1. Subjects

A total of 36 Long Evans (18 male and 18 female) rats were used in the behavioral studies. All rats were derived from six litters (and dams) received from Harlan Laboratories (Indianapolis, IN) when the pups were seven days old. Data from one male and female pup per dose group per litter were included in the behavioral analyses. Pups were given subdermal injections of ink in their paws for identification purposes on PND 10. All pups were weaned on PND 21, given a single ear punch, and housed three per cage with members of the same sex. Housing cages were clear polypropylene cages (51 cm long × 26.5 cm wide × 32 cm high) with metal tops containing food and a water bottle that were available to the animals ad libitum. The lighting in the housing room for the rats was kept on a 12 hour on/off schedule with lights on at 06:30. Drug treatments and testing were performed between 08:00 and 14:00. The principles of laboratory animal care and all experimental procedures were carried out according to the Current Guide for the Care and Use of Laboratory Animals (USPHS) under a protocol approved by the Northern Kentucky University Institutional Animal Care and Use Committee.

2.2. Daily risperidone administration

All rats received daily subcutaneous drug injections from PND 14 through PND 42. Rats received injections of 1.0 mg/kg of risperidone, 3.0 mg/kg of risperidone, or the vehicle used for the risperidone solution as a control. When the litters were weaned, rats were assigned to cages such that there was one rat from each treatment group represented within each cage. The National Institute of Mental Health's Chemical Synthesis and Drug Supply program kindly provided the risperidone. The risperidone solution was made by first dissolving it in 10% glacial acetic acid. The resulting solution was brought to volume with saline, and the pH adjusted to ~6.2 with 6 M NaOH. New solutions were made once a week. Solutions were injected at a volume of 2.0 ml/kg of body weight. Daily injections occurred in a room just outside of the housing room immediately after each rat was weighed. The doses were selected on the basis of research demonstrating that developmental administration of these doses leads to behavioral changes during adulthood (Bardgett et al., 2013) and alters neurotransmitter receptor binding (Choi et al., 2009, 2010; Moran-Gates et al., 2007).

2.3. Plasma risperidone concentrations

Because this study considered the effects of risperidone on social interactions at 1 and 23 h post-injection, the plasma concentrations of risperidone and its active metabolite, 9-OH-risperidone were determined at 1, 5, and 23 h post-injection at PND 14. Thirty-six Long–Evans rats (16 males and 20 females), derived from six litters, were used. Rats received subcutaneous injections of risperidone and were rapidly decapitated at one of the three time points. Trunk blood was collected into ice-cold tubes. Plasma was obtained from centrifugation, and stored at −70 °C until assayed. Because of the low volume of plasma from each rat pup, samples were pooled from two pups that were from different litters. Risperidone and 9-hydroxyrisperidone were detected using a modified liquid chromatographic method (LeMoing et al., 1993).

2.4. Maternal–offspring interactions

Observations of maternal–offspring interactions took place in the animal housing room between PNDs 14–17. Each pup was observed once over this four-day period at 1 h and 23 h post-drug administration, and always within the same day. Twelve rats were observed on PND 14, ten rats were observed on PNDs 15 and 16, and four rats were observed on PND 17. Approximately equal numbers of rats per risperidone administration group and sex were observed each day. Each session involved a 20-minute observation of two pups from different treatment groups with their dam in the home cage. During this session, the other littermates were placed in a separate cage in a different room. The standard cage top was replaced with a clear Plexiglas top to allow for video recording. The two pups were labeled with either a large 'X' or 'O' for identification purposes with a black permanent marker. Each pup was observed for 20 s in an alternating manner with a 10 second break between observations such that each pup was observed twenty times within the 20-minute session.

The home cage was placed on a table within the housing room and behavior within the cage was recorded with a Canon digital video camcorder centered above the cage. For each 20 second observation,