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Early-life risperidone enhances locomotor responses to amphetamine during adulthood

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ABSTRACT

Antipsychotic drug prescriptions for pediatric populations have increased over the past 20 years, particularly the use of atypical antipsychotic drugs such as risperidone. Most antipsychotic drugs target forebrain dopamine systems, and early-life antipsychotic drug exposure could conceivably reset forebrain neurotransmitter function in a permanent manner that persists into adulthood. This study determined whether chronic risperidone administration during development modified locomotor responses to the dopamine/norepinephrine agonist, D-amphetamine, in adult rats. Thirty-five male Long-Evans rats received an injection of one of four doses of risperidone (vehicle, .3, 1.0, 3.0 mg/kg) each day from postnatal day 14 through 42. Locomotor activity was measured for 1 h on postnatal days 46 and 47, and then for 24 h once a week over the next two weeks. Beginning on postnatal day 75, rats received one of four doses of amphetamine (saline, .3, 1.0, 3.0 mg/kg) once a week for four weeks. Locomotor activity was measured for 27 h after amphetamine injection. Rats administered risperidone early in life demonstrated increased activity during the 1 and 24 h test sessions conducted prior to postnatal day 75. Taking into account baseline group differences, these same rats exhibited significantly more locomotor activity in response to the moderate dose of amphetamine relative to controls. These results suggest that early-life treatment with atypical antipsychotic drugs, like risperidone, permanently alters forebrain catecholamine function and increases sensitivity to drugs that target such function.

1. Introduction

Antipsychotic drugs have been commonly used to treat psychotic disorders in adults for several decades (Olfson et al., 2012). More recently, a variety of disorders in children have been increasingly managed with prescriptions of newer, second-generation antipsychotic drugs (Lohr et al., 2015; Olfson et al., 2012, 2015). Over the last two decades throughout Europe and North America, the number of antipsychotic drug prescriptions to children under the age of 14 has increased at a greater rate than that reported for adults (Bachmann et al., 2014; Kalverdijk et al., 2008; Murphy et al., 2013; Olfson et al., 2012). At the same time, the average duration of antipsychotic drug treatment in children has become significantly longer (Kalverdijk et al., 2008).

The most commonly prescribed antipsychotic drug for children is risperidone, which predominantly targets serotonin 5-HT_{2A} and dopamine D_2 receptors, along with dopamine D_3, D_4, adrenergic α_1 and α_2, and histamine H_1 receptors (Mailman and Murthy, 2010). Animal studies have revealed alterations in neural and behavioral functions, especially those linked to dopamine, due to early-life risperidone administration. For example, daily risperidone administration for four weeks up-regulates dopamine D_2 and D_4 receptors in several forebrain regions in juvenile and adult rats but only elevates dopamine D_1 receptors in the nucleus accumbens and caudate putamen in the younger group (Moran-Gates et al., 2007). At a behavioral level, daily risperidone administration between postnatal days 14–42 leads to hyperactivity that lasts for several months after cessation of treatment (Bardgett et al., 2013). These findings raise concerns that early-life risperidone administration could lead to an enhancement in behavioral sensitivity to drugs that target dopamine synapses during adulthood.

This study evaluated the effects of early-life risperidone administration on the locomotor activity produced by the well-characterized psychostimulant, amphetamine, in young adult rats. At a neurochemical level, amphetamine increases dopamine release, blocks dopamine and norepinephrine reuptake, and inhibits monoamine oxidase from disintegrating dopamine in the synapse (see Iversen et al., 2008 for review). Amphetamine is believed to stimulate motor activity via its action in the nucleus accumbens and caudate putamen, with low doses elevating locomotion and higher doses eliciting stereotypy, due to drug effects in each respective brain region (Kelly et al., 1975). Additionally,

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White and White (2006), using moderate to high doses of amphetamine, revealed a time- and dose-dependent pattern of amphetamine-induced activity, with an increase in locomotor activity observed for 6 h post-administration, succeeded by a temporary hypoactivity that was most marked in their study at 20 h post-administration.

Since risperidone administration during postnatal development elevates forebrain dopamine receptor density (Moran-Gates et al., 2007), it was hypothesized that early-life risperidone administration would significantly augment both the hyper- and hypo-locomotor effects of amphetamine later in life. It was also expected that the administration of the higher doses of amphetamine would elicit stereotypy over the first few hours post-injection, and that this effect would be magnified in rats administered risperidone early in life.

2. Materials and methods

2.1. Subjects

Thirty-five Long-Evans male rats were used. Nine pregnant mothers were purchased from Harlan Bioproducts (Indianapolis, IN) and arrived in the animal facility on gestational day 14. On postnatal day 8, pups were identified by sex, and litters culled to four males. Rats were weaned on postnatal day 21. Upon weaning, rats were housed 2–3 per cage with continuous access to food and water. A schedule of all of the experimental events and corresponding postnatal ages is presented in Table 1. The lights in the housing room were on between 6:00 a.m. and 6:00 p.m. The Northern Kentucky University Institutional Animal Care and Use Committee approved all of the proposed procedures and animal care.

2.2. Drugs

Each of the four risperidone dose groups (vehicle, .3, 1.0, and 3.0 mg/kg of body weight; n = 9, 9, 9, and 8, respectively) contained one male rat from each of the nine litters (one of the rats from the 3.0 mg/kg dose group died at postnatal day 21 due to a failure to gain weight). The doses of risperidone were based on our previous behavioral work (Bardgett et al., 2013; Gannon et al., 2015; Stevens et al., 2016) and reports from others demonstrating the effects of early-life risperidone on neurotransmitter receptor levels (Choi et al., 2009, 2010; Moran-Gates et al., 2007). Beyond these precedents, the 1.0 mg/kg dose was selected because it acutely reduces amphetamine-induced hyperactivity by 50% (a powerful preclinical predictor of antipsychotic drug activity) (Arnt, 1995) and occupies 60–80% of dopamine D_2 receptors in rat forebrain – a degree of receptor blockade associated with antipsychotic drug efficacy in humans (Kapur et al., 2003). Nonetheless, this dose does not consistently produce drug blood levels in adult rats that approximate those observed in adult humans maintained on risperidone (Kapur et al., 2003). With this concern in mind and cognizant that some children undoubtedly receive doses above those recommended even for adults, a 3.0 mg/kg of risperidone was included for study.

Rats were weighed and administered subcutaneous injections of risperidone daily from postnatal day 14 through 42. This developmental period in the rat corresponds to the time between early childhood and late adolescence in humans (Andersen, 2005; Spear, 2000) – ages at which pediatric populations are likely to receive antipsychotic drug treatment (Constantine et al., 2011; Olfson et al., 2012). Given that many young children receive antipsychotic drugs continuously over long periods of time (Constantine et al., 2012; Kalverdijk et al., 2008), the approach used here in rats was intended to mimic prolonged antipsychotic drug exposure during development in humans.

Risperidone was dissolved in a small volume of 10% glacial acetic acid, brought to volume with .9% saline, and adjusted to a pH ~ 6.2 with 1 M sodium hydroxide. Injections were administered at a volume of 2.0 ml/kg of body weight. The National Institute of Mental Health's Chemical Synthesis and Drug Supply program kindly provided the risperidone.

D-amphetamine (Sigma) was dissolved in .9% saline. Amphetamine was injected subcutaneously once a week for four weeks as described below. Four doses of amphetamine were used (saline, .3, 1.0, and 3.0 mg/kg of body weight) at a volume of 1 ml/kg. These doses were based on the work of White and White (2006) that showed respective hyper- and hypo-activating effects of these doses over a 33-h session.

2.3. Locomotor activity

Locomotor activity was measured in a clear polypropylene cage (51 cm long × 26.5 cm wide × 32 cm high) with a wire top and inserted into a *SmartFrame* Cage Rack (Kinder Scientific, Poway, CA). Prior to testing, rats from the four treatment groups were equally divided into three testing squads. Locomotor activity was defined as the number of photobeam breaks recorded during each time bin, which varied from 5 min to one h depending on the experiment.

Locomotor activity was tabulated every 5 min over a 60-min period on postnatal days 46 and 47. Testing occurred between noon and 4:00 p.m. each day. These tests determined if rats administered risperidone early in life were more active several days after the end of the risperidone administration on postnatal day 42, as reported previously (Bardgett et al., 2013).

Over the next two weeks, rats were tested over 24 h to assess

Table 1
Experimental timetable.

Postnatal day	Activity	Description
8		Each litter culled to four males.
14		Begin daily subcutaneous injections with vehicle or risperidone (.3, 1.0 or 3.0 mg/kg). n = 9, 9, 9, or 8 rats per respective group.
21		Wean litters, house rats 2–3 per cage
42		Last injection of risperidone or vehicle
46 and 47	Spontaneous locomotion	Test locomotor activity in each rat for one h each day.
55, 56, or 57	Circadian locomotion	Test locomotor activity in each rat for 24 h on one of the three days listed. Same procedure is repeated one week later on day 62, 63, or 64.
62, 63, or 64	Circadian locomotion	
75, 77, or 79	Locomotor response to amphetamine	Test activity for 30 min prior to and 27 h after subcutaneous injection of saline or one of three doses (.3, 1.0, or 3.0 mg/kg) of amphetamine. During each of the four weeks, each rat tested on only one of the three days listed. On each of the four weeks, the same procedure is conducted except that each rat receives a different amphetamine dose than it did on any of the other weeks.
82, 84, or 86	Locomotor response to amphetamine	
89, 91, or 93	Locomotor response to amphetamine	
95, 97, or 99	Locomotor response to amphetamine	