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Effects of risperidone and paliperidone pre-treatment on locomotor response following prenatal immune activation

Neil M. Richtand [a,b,c,*], Rebecca Ahlbrand [a,b], Paul Horn [a,d], Kevin Stanford [b], Stefanie L. Bronson [b,c], Robert K. McNamara [b,c]

[a] Cincinnati Veterans Affairs Medical Center, Psychiatry Service (V116A), 3200 Vine Street, Cincinnati, OH 45220, United States
[b] Department of Psychiatry, University of Cincinnati College of Medicine, 231 Albert Sabin Way, ML0583, Cincinnati, OH 45267, United States
[c] Neuroscience Graduate Program, University of Cincinnati, Cincinnati, OH 45267, United States
[d] Department of Mathematical Sciences, University of Cincinnati, Cincinnati, OH 45221, United States

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ABSTRACT

Aim: Limited data are available regarding pharmacological characteristics of effective interventions for psychosis prevention. Enrollment challenges in psychosis prevention trials impede screening diverse interventions for efficacy. Relevant animal models could help circumvent this barrier. We previously described prevention with risperidone of abnormal behavior following neonatal hippocampal lesion. We aimed to extend those findings evaluating risperidone and paliperidone following prenatal immune activation, a developmental model of a schizophrenia risk factor. We evaluated a later developmental time point to determine persistent effects of drug treatment.

Methods: Pregnant Sprague–Dawley rats were injected with poly I:C or saline on gestational day 14. Offspring of poly I:C and saline-treated dams received risperidone (0.45 mg/kg/d), paliperidone (0.05 mg/kg/d), or vehicle from postnatal days 35–70. Locomotor responses to novelty, saline injection, and amphetamine (1 and 5 mg/kg) were determined at three months, i.e., 21 days following antipsychotic discontinuation.

Results: Risperidone and paliperidone had persistent effects on behavioral response to amphetamine (1 mg/kg) at 3 months, ameliorating the impact of prenatal immune activation on offspring of poly I:C-treated dams. Risperidone, but not paliperidone, also exerted persistent effects in offspring of saline-treated dams on locomotor response to saline and amphetamine (5 mg/kg) injection.

Conclusions: Risperidone and paliperidone pre-treatment of poly I:C offspring during peri-pubertal development stabilized response to amphetamine exposure persisting into early adulthood. Prenatal immune activation provides a model for evaluating effects of an environmental risk factor for schizophrenia, and has potential utility for identifying pharmacological approaches to early intervention.

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1. Objectives of the study

Several factors impede identification of effective primary prevention treatments for first-episode psychosis. First, the most effective primary prevention interventions would target the etiology of the illness. At present the etiological factors causing schizophrenia and other psychotic disorders are unknown, necessitating screening many compounds to identify effective candidates for primary prevention. In practice the risk to human subjects, as well as limited clinical trial enrollment, make it difficult to screen multiple compounds and dosages in human subjects. Second, medication compliance in long-term adolescent and young adult studies is typically poor. For example, less than 50% of subjects were fully adherent with medication treatment in a study evaluating risperidone efficacy in first-episode psychosis prevention (McGorry et al., 2002). This confound increases the likelihood of failing to detect beneficial effects of preventive treatment. Third, rather than preventing development of psychotic symptoms, treatment interventions may merely delay their appearance. Adequately addressing this question requires following a large number of subjects over an extended length of time, a study design which is exceedingly difficult to accomplish in an adolescent or young adult human

* Corresponding author. University of Cincinnati College of Medicine, 231 Albert Sabin Way, ML0583, Cincinnati, OH 45267. Tel.: +(513) 558 6657; fax: +(513) 558 0042.
E-mail address: neil.richtand@uc.edu (N.M. Richtand).

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sample, but can be directly studied in animals. Because of the tremendous human and economic burden of schizophrenia, primary prevention modalities of even modest impact would likely have significant public health consequence, and a growing number of studies have examined preventive treatment for individuals at high risk of developing first-episode psychosis (McGorry et al., 2002; Cannon et al., 2008; Cornblatt et al., 2007; Addington et al., 2007; Woods et al., 2007, 2003; McGlashan et al., 2006; McGlashan, 1996; Tsuang et al., 2002; Cornblatt, 2002; Morrison et al., 2004; Hafner et al., 2004). In combination, these studies suggest that for many prodromal patients clinical need provides a rationale for early intervention, and that effective preventive intervention appears to be a feasible goal. The limited information regarding pharmacological characteristics of effective intervention underscores the compelling need for animal models with predictive validity in the first-episode psychosis prevention field.

We previously observed a preventive effect of risperidone (postnatal days 35–56) in the neonatal hippocampal lesion developmental model of abnormal rat behavior (Richtand et al., 2006). We sought to extend those findings by determining 1.) if risperidone and its pharmacologically active metabolite paliperidone have a similar protective effect following prenatal immune activation, an independent animal model with relevance to schizophrenia, and 2.) if the protective effect extended beyond medication discontinuation. We hypothesized that early developmental treatment with risperidone and paliperidone would result in a longstanding modification, preventing expression of behavioral abnormalities of prenatal immune activation following medication discontinuation in later adulthood. Protective effects of clozapine, haloperidol, and fluoxetine on development of behavioral abnormalities following prenatal immune activation have been previously described (Meyer et al., 2008b). Additionally, protective effects of both clozapine (Piontkewitz et al., 2009) and risperidone (Piontkewitz et al., 2010) against the emergence of structural and behavioral abnormalities following prenatal immune activation have been observed. In combination, these preclinical studies demonstrate the utility of animal model studies to identify potential early pharmacological interventions against schizophrenia.

The prenatal immune activation model is a developmental model of abnormal rodent behavior based upon observations from epidemiological studies suggesting exposure to maternal infection increases schizophrenia risk (Mednick et al., 1988; Brown and Derkits, 2010; Takei et al., 1994, 1996; Brown, 2006; Penner and Brown, 2007; Wright and Murray, 1993; Brown et al., 2004; Limosin et al., 2003; Murray et al., 1992). Prenatal viral infection of mice resulted in the development of abnormalities directly relevant to those observed in schizophrenia, including deficits in prepulse inhibition of startle and social interactions. Furthermore, key alterations resulted from the maternal immune response rather than the virus itself, as a prepulse inhibition of startle deficit was induced in the absence of viral infection by injection of the synthetic double-stranded RNA polyinosinic–polycytidylic acid (poly I:C) (Shi et al., 2003). Subsequent studies in multiple laboratories have identified cellular, neurochemical, structural, behavioral, and cognitive alterations of relevance to schizophrenia following prenatal immune activation with poly I:C, the bacterial endotoxin lipopolysaccharide (LPS), and with direct injection of pro-inflammatory cytokines [recently reviewed in (Boksa, 2010; Meyer and Feldon, 2009, 2010; Patterson, 2009)]. Longstanding behavioral abnormalities, including increased locomotor responsiveness to stress, novel environment, and amphetamine and deficits in prepulse inhibition of startle have been observed after puberty in rodents following prenatal immune activation (Meyer et al., 2008a, b, 2005; Shi et al., 2003; Ozawa et al., 2006; Romero et al., 2007; Zuckerman et al., 2003). Subsequent to prenatal immune activation rodents also exhibit deficits in social behavior (Shi et al., 2003) and cognition (Meyer et al., 2005; Ozawa et al., 2006; Bitanihirwe et al., 2010) which may be analogous to the negative and neurocognitive deficits, respectively, observed in schizophrenia patients. Because the underlying etiology; time course of development of abnormal behaviors; and some of the behaviors themselves, share similarities with schizophrenia, treatments inhibiting behavioral alterations using this animal model could have predictive validity in identifying primary preventive treatments for schizophrenia and first-episode psychosis. Here we report that both risperidone and paliperidone prevent altered locomotor response to amphetamine in adult offspring of maternal immune-activated rats.

2. Materials and methods

2.1. Animals

A summary of the experimental design is shown in Fig. 1. Nulliparous female Sprague–Dawley rats for use as breeders were obtained from Harlan Laboratories (Indianapolis, IN) and male breeders were generated within our facility. Following a minimum of two weeks acclimatization to the housing facility, males and females were co-housed overnight, with the following morning defined as gestational day 0. Pregnant rats (identified by weight gain of $\geq$40 g) were injected with the synthetic nucleic acid analogue poly I:C (Sigma P1530; 8 mg/kg, i.p.) or saline (1 ml/kg) on gestational day 14, in order to stimulate a maternal inflammatory response. The poly I:C dosage was chosen based upon dosage ranges used by other investigators for rat intraperitoneal injection [range of dosages reported 0.75 mg/kg to 20 mg/kg; mean dose 10 mg/kg (Fortier et al., 2004; Gilmore et al., 2005)]. Based upon previous studies describing anorexia and weight loss associated with maternal immune activation (Zuckerman et al., 2003; Fortier et al., 2004), pregnant dams were weighed on gestational days 14 and 15 to determine the presence or absence of weight loss. All poly I:C-treated dams experienced weight loss of 3 or more grams. This screening method was used because weight loss in poly I:C-treated dams during the 24 h following poly I:C injection predicts the

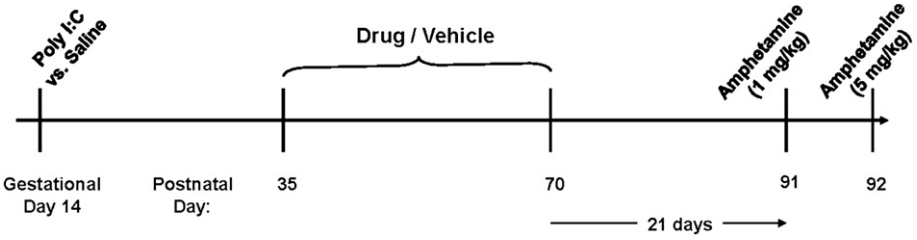

Fig. 1. Experimental design summary: Pregnant dams received poly I:C or saline injection on gestational day 14. Male and female offspring received drug or vehicle treatment in drinking water on postnatal days 35–70. Behavioral testing was performed at 3 months of age.