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Effects of Risperidone and Paliperidone Pretreatment on Locomotor Response Following Prenatal Immune Activation

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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 to 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.

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Conclusions—Risperidone and paliperidone pretreatment 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.

Keywords

maternal; schizophrenia; animal model; first-episode psychosis; prodrome; dopamine

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 [1]. 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 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 [1–12]. 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 [13]. 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 [14]. Additionally, protective effects of both clozapine [15] and risperidone [16] 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 [17–26]. 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 alterationsresulted 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) [27]. 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 [28–31]]. 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 [27;32–37]. Subsequent to prenatal immune activation rodents also exhibit deficits in social behavior [27] and cognition [32;35;38] 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.

Materials and Methods

Animals

A summary of the experimental design is shown in Figure 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 ≥ 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 [39;40]]. Based upon previous studies describing anorexia and weight loss associated with maternal immune activation [37;39], 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 hours following poly I:C injection predicts the amphetamine-stimulated locomotor response in adult offspring, as locomotor activity of poly I:C treated dams without weight-loss was not different from locomotor activity of offspring of saline-treated dams [41]. Offspring from two poly I:C-treated dams and one saline-treated dam were excluded based on these weight change criteria.

Offspring were weaned on postnatal day 21 and housed 2–3/cage with same sex siblings. Animals were maintained at all times on the same 12-hour light:dark cycle (0600 on; 1800 off). All animal procedures were conducted in agreement with the Guide for the Care and Use of Laboratory Animals in accordance with NIH guidelines, and were approved by the

Cincinnati Department of Veterans Affairs Medical Center Institutional Animal Care and Use Committee.

Drug treatment

Male and female rat pups were randomly assigned at birth to treatment with risperidone (0.45 mg/kg/day), paliperidone (0.05 mg/kg/day) or vehicle via drinking water from postnatal days (PD) 35 to 70. Group sizes were balanced for sex. Group sample sizes were poly I:C/veh: n=13, poly I:C/risp: n=21, poly I:C/pali: n=13; saline/veh: n=31, saline/risp: n=14, saline/pali: n=21. All experimental animals were born within a six-week period. The risperidone dosage was chosen to be within the approximate bioavailability range of the risperidone dosage providing a protective effect via subcutaneous route of administration following neonatal hippocampal lesion [13]. Paliperidone is a metabolite of risperidone, with high affinity binding at serotonin 5-HT_{2A} and dopamine D_2 receptors. The paliperidone dosage was selected to evaluate a lower dose range than the risperidone dose in order to explore the potential for greater potency for paliperidone relative to risperidone in this assay. The drug treatment period was selected in order to provide drug treatment throughout puberty. In the rat, postnatal days 23 through approximately 42 are the period of pre-puberty, and postnatal days ~ 45 through postnatal day 60 represent the pubertal period of sexual maturation [42–45]. Animals received drug treatment administered in drinking water as previously described [46–48] in order to avoid the stress of repeated subcutaneous injections, or stress associated with the surgical implantation of minipumps. Drug administration in drinking water permits maintenance of drug dose in accordance with age-related increases in body weight, and mimics oral administration in human patients. In more detail, following the general method of Parikh and colleagues [46], risperidone stock solutions (0.1 mg/ml) and paliperidone stock solution (0.01 mg/ml) were prepared in 0.26 mM acetic acid in water. Daily weight and water consumption were measured for each animal, and the necessary volume of drug or vehicle stock solution was provided in the animal's water bottle to supply the appropriate drug dosage.

Risperidone and paliperidone powder were from Ortho-McNeil Janssen. D-amphetamine sulfate (Sigma, St. Louis, MO) was dissolved in 0.9% saline. Amphetamine concentration is described as free base. All injections were in a final volume of 1 ml/kg.

Behavioral Testing

Behavioral testing was performed in 30 Residential Activity Chambers as we have previously described [49]. Each RAC comprises a lighted, ventilated, sound-attenuated cabinet housing a 16″×16″×15″ Plexiglas enclosure. Locomotion was monitored with a 16×16 photo beam array (San Diego Instruments, San Diego, CA) located 0.5 inches above the floor of the enclosure. Locomotion is expressed as crossovers, defined as entry into any of the active zones of the chamber, as we have previously described [49]. Data were collected in ten-minute bins for behavioral analyses. Animals were maintained throughout behavioral testing on the same 12-hour light/dark cycle (0600 on; 1800 off) with ad lib access to food and water. Testing began at 3 months of age, i.e., 21 days following antipsychotic discontinuation. On Day 1 of testing between 0900 and 1000, animals were placed into the Residential Activity Chambers and locomotor response during the first hour in the novel environment was determined. Animals were then injected with saline (1.0 ml/kg subcutaneous), and locomotion response to injection was monitored for one hour. Animals were then injected with amphetamine (1.0 mg/kg subcutaneous), and locomotion recorded. They remained in the testing chambers overnight. The following day (Day 2) between 0900 and 1000, animals were injected with a higher amphetamine dose (5 mg/kg subcutaneous), and locomotion recorded. The two different amphetamine dosages were selected for study based upon prior data characterizing the rat locomotor response to amphetamine in order to observe both

direct locomotion (1 mg/kg amphetamine dose) as well as post–stereotypy locomotion (5 mg/kg amphetamine dose) effects[50].

Statistical analysis

Locomotor data were log-transformed and analyzed by three-way ANOVA with repeated measures, with Pre-treatment (Poly I:C vs. Saline), Post-treatment (Risperidone vs. Paliperidone vs. Vehicle) and Sex as main factors, Time (10-minute interval) as the repeated measure, and locomotion as dependent measure using the MIXED procedure of SAS System for Windows, (SAS Institute, Cary, NC) with statistical significance set at $p < .05$. Subsequent multiple comparisons of main effects between treatment groups were conducted by post hoc analysis using the Tukey-Kramer test. Where significant interactions with Time were identified, further analyses of simple effects were conducted (slice ANOVA) using the MIXED procedure and slice option. Treatment effects within each 10-minute interval were subsequently adjusted together for multiple planned comparisons by False Discovery Rate (error rate = 0.05). For all analyses, treatment differences were considered statistically significant at $p < 0.05$.

Results

Locomotor response to novelty

In agreement with previous investigators [35;37], ANOVA did not identify a significant Sex interaction with Pre-treatment or Post-treatment effects on novelty-stimulated locomotion, and therefore behavioral response of both sexes was combined in analysis of group effects. ANOVA identified significant effects of time [$F(1,107) = 979.42$, $P < .0001$], post-treatment [$F(2,102) = 3.42$, $P = .037$] and a trend towards Post-treatment × time interaction [$F(2,107) = 3.08$, $P = .05$]. ANOVA did not identify a significant Pre-treatment × time interaction ($P = .081$), Pre-treatment × post-treatment × time interaction ($P = .30$), or Pre-treatment × Post-treatment interaction ($P = .10$).

Risperidone—The effect of risperidone pretreatment on locomotor response to a novel environment is shown in Figure 2, left panel. Post hoc comparisons showed locomotor response to novelty of rats given risperidone vs vehicle differed significantly ($P = .003$). Post-hoc Tukey-Kramer tests suggest this difference results from effects of risperidone on poly I:C offspring, as locomotor response to novelty of poly I:C rats given risperidone vs vehicle differed significantly (Poly I:C/Veh vs Poly I:C/Risp $P = .01$; Poly I:C/Veh vs Sal/Risp $P = .011$). Risperidone had no significant effect, however, on offspring of saline-treated dams (Sal/Veh vs Sal/Risp $P = .79$). There were no significant differences between poly I:C offspring given risperidone, and offspring of saline-treated dams given vehicle or risperidone (Poly I:C/Risp vs Sal/Veh $P = .88$; Poly I:C/Risp vs Sal/Risp $P = 1.0$).

Paliperidone—The effect of paliperidone pretreatment on locomotor response to a novel environment is shown in Figure 3, left panel. Paliperidone had no significant effect on adult offspring of poly I:C-treated dams (Poly/Veh vs Poly/Pali $P = 0.93$) or saline-treated dams (Sal/Veh vs Sal/Pali $P = 1.0$). However, locomotor response to novelty of all rats (poly I:C and saline) given risperidone vs paliperidone differed significantly (Risp vs Pali $P = .039$).

Locomotor response to saline injection

ANOVA identified a significant Sex interaction with the Pre-treatment effect of Poly I:C [$F(1,101) = 4.86$, $P = .03$], however Post-hoc Tukey-Kramer tests demonstrated no differences in comparisons between relevant groups. ANOVA did not identify a significant Sex interaction with Post-treatment effects of drug on saline injection-stimulated locomotion. Therefore, behavioral response of both sexes was combined in analysis of group effects.

ANOVA identified a significant effect of time [F (1,107) = 574.07, P < .0001], and Post-treatment × time interaction [F (2,107) = 8.27, P = .0005], but did not identify significant effects of Pre-treatment × time (P = .51); Pre-treatment × post-treatment interaction (P = .09); or Pre-treatment × post-treatment × time interactions (P = .084).

Risperidone—Locomotor response to saline injection is illustrated in Figure 2 (middle panel). Locomotor response to saline injection of all rats (poly I:C and saline) given risperidone vs vehicle differed significantly (P < .0001). Post-hoc Tukey-Kramer tests identified a significant effect of risperidone on offspring of saline-treated dams [(Sal/Veh vs Sal/Risp P = .0005); (Poly I:C/Veh vs Sal/Risp P = .0055)]. Post-hoc Tukey-Kramer tests did not identify significant differences in other comparisons [(Poly I:C/Risp vs Sal/Veh P =.17); (Poly I:C/Veh vs Sal/Veh P = 1.0); (Poly I:C/Veh vs Poly I:C/Risp P =.37); (Poly I:C/Risp vs Sal/Risp P =.31)].

Paliperidone—The effect of paliperidone pretreatment on locomotor response to a saline injection is shown in Figure 3, middle panel. Locomotor response to saline injection of all rats (poly I:C and saline) given paliperidone vs risperidone differed significantly (P < .0001). In contrast, locomotor response to saline injection of rats given paliperidone vs vehicle were not significantly different (P =.89).

Locomotor response to amphetamine (1 mg/kg)

ANOVA identified a significant Sex interaction with Pre-treatment and Post-treatment effects on amphetamine-stimulated locomotion [F (2,101) = 3.53, P = .033], however Post-hoc Tukey-Kramer tests demonstrated no differences in comparisons between relevant groups and therefore behavioral response of both sexes was combined in analysis of group effects. ANOVA identified a significant effect of time [F (1,107) = 50.97, P <.0001], Pre-treatment × post- treatment × time interaction [F (2,107) = 4.26, P =.017], and a significant main effect of Post-treatment [F (2,95) = 3.11, P =.049]. ANOVA did not identify a significant Pre-treatment × time interaction (P = .17) or Pre-treatment × Post-treatment interaction (P =.48).

Risperidone—Post-hoc Tukey-Kramer tests identified significant effects of 1.) prenatal immune activation on behavior, and 2.) risperidone ameliorating the impact of prenatal immune activation on behavioral outcome. As shown in Figure 2, locomotor response of poly I:C and saline offspring given vehicle differed significantly (P = .044), with amphetamine-stimulated locomotion lower in offspring of poly I:C treated dams. The effect of poly I:C on locomotor response was ameliorated by risperidone post-treatment during postnatal days 35–70. Locomotor response of Poly I:C offspring given risperidone vs vehicle differed significantly (P = .024), while behavior of poly I:C offspring given risperidone and offspring of saline-treated dams given vehicle were similar (P = 1.0). Of note, risperidone had no significant effect on adult offspring of saline-treated dams (P = 0.17).

Paliperidone—As shown in Figure 3, amphetamine-stimulated locomotion was lowered in offspring of poly I:C treated dams, and this effect of poly I:C on locomotor response was ameliorated by paliperidone (0.05 mg/kg/day) post-treatment during postnatal days 35–70. Post-hoc Tukey-Kramer tests identified highly significant effects of paliperidone ameliorating the impact of poly I:C on behavioral outcome. Locomotor response of poly I:C offspring given paliperidone (0.05 mg/kg/day) vs vehicle differed significantly (P = .0003), while behavior of poly I:C offspring given paliperidone and offspring of saline-treated dams given vehicle were similar (P = .18). Paliperidone had no significant effect on adult offspring of saline-treated dams (P = 0.68).

Locomotor response to amphetamine (5 mg/kg)

Risperidone—Risperidone's influence on locomotor response to a higher amphetamine dose (5 mg/kg) is shown in Figure 4. The rat behavioral response to high-dose amphetamine (5 mg/kg) is complicated by the simultaneous expression of two competing behaviors, locomotion and stereotypy, with an initial period of elevated locomotion (intervals 1–2 in Figure 4) followed by a period of elevated stereotypy, evidenced as decreased locomotion. The period of stereotyped behavior is then followed by a post-stereotypy period of elevated locomotion [50;51]. As shown in Figure 4, poly I:C animals treated with vehicle or risperidone transition from the initial elevated locomotion period into stereotypy (reduced locomotion) more rapidly than offspring of saline-treated dams. Both Saline/Vehicle and Poly I:C/risperidone animals emerge from stereotypy more rapidly than the other two groups, and display a similar post-stereotypy locomotion phase. In contrast, Saline/Risperidone rats display elevated post-stereotypy locomotion. In order to analyze the periods of predominantly stereotyped behavior and predominantly elevated locomotion separately, behavioral data were analyzed by ANOVA separately for intervals 0 through 20, and 21 through 40. ANOVA did not identify a significant interaction of Sex with the Pre-treatment effect on amphetamine-stimulated locomotion, and therefore behavioral response of both sexes was combined in analysis of group effects. For intervals 0 through 20 ANOVA identified a significant effect of time [$F(1,107) = 117.37$, $P < .0001$]; Pre-treatment × Post-treatment × time interaction [$F(2,107) = 4.31$, $P = .016$]; Pre-treatment × Post-treatment interaction [$F(2,101) = 5.72$, $P = .004$]; and Pre-treatment × time interaction [$F(1,107) = 17.52$, $P < .0001$)]. Post-hoc Tukey-Kramer tests did not identify significant differences between treatment groups for the initial 20 intervals. For intervals 21 through 40, ANOVA identified a significant effect of time [$F(1,107) = 896.44$, $P < .0001$], and Post-treatment × time interaction [$F(2,107) = 4.56$, $P = .013$)]. The effect of Post-treatment [$F(2,105) = 2.59$, $P = .08$], and Pre-treatment × Post-treatment × time interaction were not statistically significant [$F(2,107) = 1.73$, $P = .18$]. Post-hoc Tukey-Kramer tests identified a significant difference in locomotor response to amphetamine 5 mg/kg injection of all rats (poly I:C and saline) given risperidone vs vehicle ($P = .013$). Saline rats treated with risperidone and vehicle differed significantly in locomotor response ($P = .006$).

Paliperidone—Paliperidone's influence on locomotor response to amphetamine (5 mg/kg) is shown in Figure 5. Poly I:C animals treated with vehicle transition from the initial elevated locomotion period into stereotypy (reduced locomotion) more rapidly than the other three treatment groups. Both Poly I:C/paliperidone and Saline/vehicle animals emerge from stereotypy more rapidly than the other two groups, while all display a similar post-stereotypy locomotion phase. Behavioral data described above were analyzed by ANOVA separately for intervals 0 through 20, and 21 through 40 as described above. Post-hoc Tukey-Kramer tests did not identify significant differences between treatment groups for the initial 20 intervals. For intervals 21 through 40, post-hoc Tukey-Kramer tests identified a significant difference in locomotor response of all rats (poly I:C and saline) treated with paliperidone and risperidone ($P < .0001$). In contrast, there was no significant difference in locomotor response of rats treated with paliperidone and vehicle ($P = .23$).

Discussion

The data presented provide evidence for longstanding consequences of exposure to the atypical antipsychotic medications risperidone and paliperidone during peri-pubertal development in offspring of both Poly I:C and saline-treated dams. Risperidone and paliperidone treatment during pre-pubertal and pubertal development altered the behavioral response of offspring of both poly I:C and saline-treated dams, and these changes persisted into early adulthood. Risperidone had a persistent effect upon the locomotor response to

novelty of offspring of poly I:C-treated dams. The blunted locomotor response to low dose amphetamine (1 mg/kg) following prenatal immune activation was normalized by prior risperidone and paliperidone treatment (Figures 2–3). In addition to long-term amelioration of behavioral abnormalities resulting from prenatal immune activation, risperidone but not paliperidone treatment also had long-lasting effects on offspring of saline-treated dams. Risperidone treatment during postnatal days 35–70 resulted in persistently elevated locomotor response to both saline injection and high dose amphetamine (5 mg/kg) in saline offspring at 3 months of age (Figures 2 and 4).

These findings are relevant to considerations of both pharmacological targets of efficacy for psychosis prevention, as well as safety issues in children at-risk but not yet ill. Because prenatal immune activation provides a developmental animal model with relevance to schizophrenia [27;32;35–37], the data further inform hypotheses regarding potential pharmacological preventive interventions for psychotic disorders. It cannot be assumed that pharmacological mechanisms responsible for longstanding behavioral effect described above are identical to those providing treatment efficacy for psychosis, or that antipsychotic drugs would be the safest or most effective primary preventive treatment for psychosis [52;53]. Based on the results of a randomized trial of risperidone in individuals at high risk for progression to first-episode psychosis, which determined that low-dose risperidone (average dose 1.3 mg/d) significantly reduced the incidence of first-episode psychosis [1], we had previously determined that risperidone pretreatment reduces abnormal hyperlocomotor response to amphetamine following neonatal hippocampal lesion [13]. That study did not distinguish between prevention, vs. suppression or postponement, of the emergence of abnormal behaviors following neonatal hippocampal lesions, since the withdrawal period between the final risperidone pre-treatment and behavioral testing was limited to one day. The current study extends those findings by using a different animal model, and later observational time point. Outcome measures were chosen to evaluate behavioral measures modulated in part by dopaminergic function: locomotor response to novelty [54–57]; locomotor response to subcutaneous saline injection, which likely is at least in part reflective of locomotor response to stress [58–60]; and locomotor response to both low and high amphetamine dosages. The behavioral response to amphetamine, which evolves from exploration and examination of the environment into more complex patterns of stereotyped behaviors, was selected because it has both face and predictive validity as an animal model of psychosis [61].

Several studies have previously evaluated the effects of antipsychotic medications in the prenatal immune activation animal model. Meyer and colleagues determined that treatment of mice during postnatal days 35 through 65 following prenatal immune activation with the orally administered antipsychotic medications clozapine or haloperidol, or with the selective serotonin reuptake inhibitor antidepressant fluoxetine, prevented the emergence of altered responsivity to amphetamine (2.5 mg/kg) in adulthood (measured between postnatal days 90 and 120). They also determined that pre-treatment with clozapine, haloperidol, and fluoxetine prevented the emergence of abnormalities in two additional behaviors with relevance to schizophrenia, prepulse inhibition of startle and latent inhibition [62]. Of particular interest in the context of safety concerns for preventive treatments administered to individuals at-risk, but not yet diagnosed with a disease, their study also observed behavioral abnormalities in normal control mice treated with drugs compared to normal control placebo-treated mice [62]. Those findings are similar to our observation of elevated locomotor response to saline injection and amphetamine (5 mg/kg) in adult control rats exposed to risperidone during peri-pubertal development (Figures 2 and 4). Protective effects of preventive treatment during postnatal days 34–47 with intraperitoneal injections of clozapine [15] and risperidone [16] have also been observed. In both studies, peri-adolescent treatment of rats following prenatal immune activation protected against the emergence of

ventricular enlargement and reduced hippocampal volume in adulthood. Antipsychotic pretreatment with clozapine and risperidone also prevented the emergence of elevated locomotor response to amphetamine in adult offspring of poly I:C treated dams. In combination, these preclinical studies demonstrate longstanding effects of early pharmacological interventions against a variety of measures with direct clinical relevance to schizophrenia.

The data presented in this paper therefore adds to a growing literature suggesting that low dosage antipsychotic medication administration during the peri-adolescent period following prenatal immune activation provides long-standing stabilization of the mesolimbic dopamine system. An important contrast between our study and previously published findings is that prenatal immune activation resulted in blunted locomotor response to amphetamine in our protocol, while adult rodents display enhanced locomotor response to amphetamine following prenatal immune activation in other published studies [reviewed in [28–31]]. We discuss this contrast below in the context of the developmental progression of dopamine system abnormalities following prenatal immune activation. Similar to the development of mesolimbic abnormalities in schizophrenia, alterations in the mesolimbic dopamine system following prenatal immune activation exhibit a developmental progression. Studies examining varying indices of dopamine function following prenatal immune activation demonstrate decreased response early in development, with a transition to elevated dopamine function in adulthood in most but not all conditions. A detailed analysis of dopamine system development identified decreased immunoreactivity for both tyrosine hydroxylase and dopamine transporter in caudate putamen, nucleus accumbens core, and nucleus accumbens shell in offspring of poly I:C injected dams relative to control mice at PD 35. In contrast, at PD 70 tyrosine hydroxylase immunoreactivity was *increased* in the core and shell subregions of the nucleus accumbens [63]. Similarly, another study observed decreased dopamine levels at postnatal day 40 following prenatal immune activation, while in early adulthood (PD 70) dopamine and DOPAC levels were similar in offspring of prenatal immune-activated and control rats [64]. Later in adulthood (beyond PD 170) dopamine levels were elevated following prenatal immune activation in one study [64], while in a second study nucleus accumbens dopamine levels remained reduced in adult offspring of rats following prenatal immune activation with a subchronic regimen of lipopolysaccharide in late pregnancy [65]. The locomotor response to stimulant drugs blocking dopamine transport follows a similar developmental progression. During the peripubertal period, locomotor response was similar in offspring of prenatal immune-activated and control dams injected with amphetamine (rats, PD 40) [37] and methamphetamine (mice, PD 35) [35]. In adult rodents, elevated locomotor response to amphetamine and methamphetamine has been observed following prenatal immune activation [34;35;37;66]. In combination, these findings suggest an adaptive interaction between a hypo-functional mesolimbic dopamine system following prenatal immune activation and the developmental environment may lead to elevated mesoaccumbens dopamine function in adulthood. The blunted response observed in this manuscript, and by Bakos et al. [65] may therefore result from either deficient dopamine function, or maturational delay in the capacity to transition to the elevated response observed by others. In either case, the current data demonstrate stabilization of mesolimbic dopamine function by both risperidone and paliperidone. Additionally, the mechanism(s) underlying this transition from hypofunction to elevated mesolimbic dopamine function has direct relevance to the etiology of convergence to psychosis. Future studies dissecting the distinct components of dopamine synthesis, release, reuptake, and individual dopamine receptor subtype contributions to the behavioral response in this model may therefore be of interest.

Methodological differences between our study and other investigations may also help identify determinants of hyper-responsive dopamine system development following prenatal

immune activation. Experimental variables which differ between prenatal immune activation studies include agent used for induction of prenatal immune activation; dose; route of administration; use of anesthesia; timing of prenatal immune activation during gestational phase; animal species and strain; and monitoring of maternal immune activation. Further study will be needed to identify whether differences in these variables between our protocol and other studies contributed to the different outcomes.

Protective mechanism(s) of action

While the mechanism(s) underlying the protective effects of risperidone and paliperidone observed in this study are not known, both risperidone and paliperidone exhibit highest affinity binding to serotonin 5-HT_{2A} receptors [67]. We have previously suggested that serotonin 5-HT_{2A} antagonist effects of risperidone underlie the protective effect following neonatal hippocampal lesion [13;68], since protective effects were observed at low risperidone dosages with predominantly serotonin 5-HT_{2A} antagonist effects. Functional connections between serotonin 5-HT_{2A} receptors and glutamate mGluR2 receptors [69] provide one plausible mechanism linking 5-HT_{2A} receptor effects with glutamate system interactions potentially involved in the developmental pathology of dopamine system abnormalities[70]. It is not known whether the differences observed between the effects of risperidone and paliperidone are due to differences in pharmacokinetics, pharmacodynamics, or differences in dosage of the two medications. Further study will be needed to elucidate the mechanism involved in the observed effects.

Summary

Prenatal immune activation may provide a useful model for evaluating both safety and efficacy of potential treatments for psychosis prevention. The findings described above highlight the utility of the prenatal immune activation model in evaluating interactions between preventive interventions, developmental vulnerabilities, and their effect upon long-term behavioral outcome. It will be of interest in future studies to evaluate other aspects of behavior with relevance to schizophrenia, such as rodent cognitive deficits observed following prenatal immune activation [27;32;35–38;71].

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none

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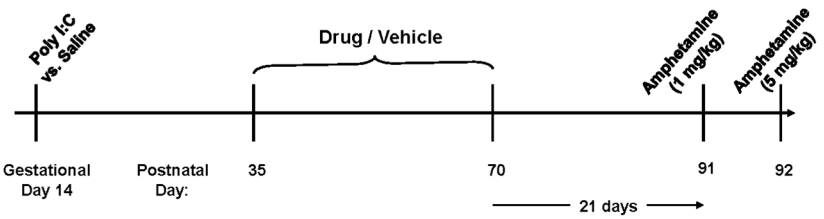

Figure 1. Experimental design summary

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.

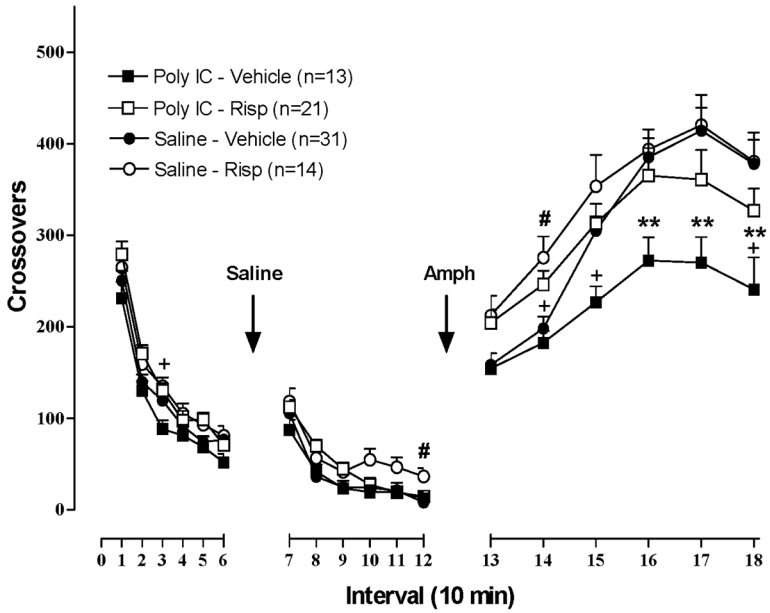

Figure 2. Effect of risperidone on locomotor response to novelty, saline injection, and low dose amphetamine (1 mg/kg) following prenatal immune activation

Statistically significant effects identified by slice ANOVA with False Discovery Rate adjustment are indicated. $^{+}$ $P < .05$ between poly I:C/Veh and Poly I:C/Risp; $^{\#}$ $P < .05$ between Sal/Veh and Sal/Risp; ** $P < .01$ between poly I:C/Veh and Sal/Veh.

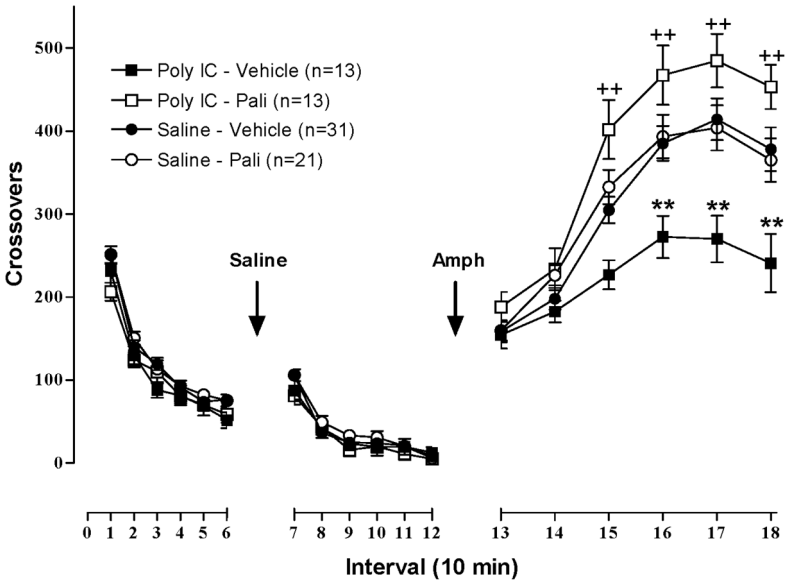

Figure 3. Effect of paliperidone on locomotor response to novelty, saline injection, and low dose amphetamine (1 mg/kg) following prenatal immune activation

Statistically significant effects identified by slice ANOVA with False Discovery Rate adjustment are indicated. ** P < .01 between poly I:C/Veh and Sal/Veh; $^{+\,+}$P < .01 between poly I:C/Veh and Poly I:C/Pali. Poly I:C/Veh and Sal/Veh groups are the same as represented in Figure 2.

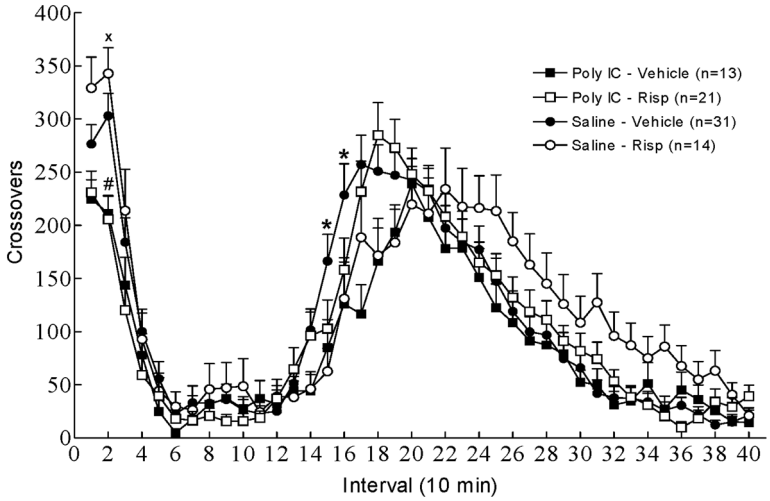

Figure 4. Effect of risperidone on locomotor response to high dose amphetamine (5 mg/kg) following prenatal immune activation

Statistically significant effects identified by slice ANOVA with False Discovery Rate adjustment are indicated. # P < .05 between poly I:C/Risp and Sal/Veh; * P < .05 between poly I:C/Veh and Sal/Veh; × P < .01 between poly I:C/Risp and Sal/Risp.

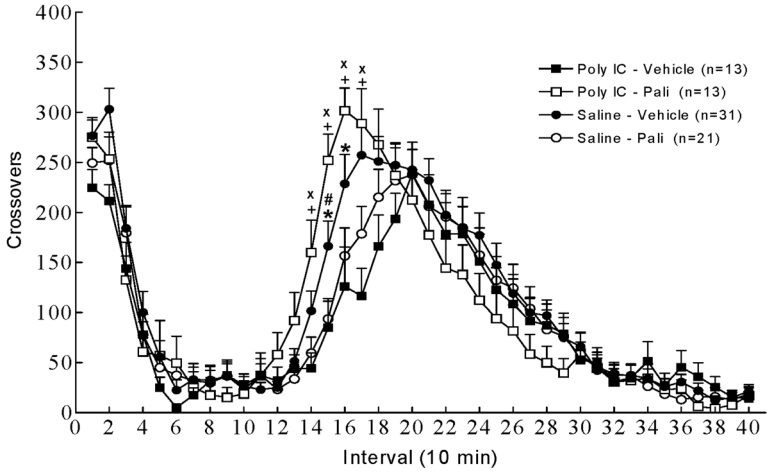

Figure 5. Effect of paliperidone on locomotor response to high dose amphetamine (5 mg/kg) following prenatal immune activation

Statistically significant effects identified by slice ANOVA with False Discovery Rate adjustment are indicated. $^{\times}$ P < .05 between poly I:C/Pali and Sal/Pali; $^{+}$ P < .05 between poly I:C/Veh and Poly I:C/Pali; * P < .05 between poly I:C/Veh and Sal/Veh; $^{\#}$ P < .05 between Sal/Veh and Sal/Pali. Poly I:C/Veh and Sal/Veh groups are the same as represented in Figure 4.