A Novel Anti-Neuroinflammatory Treatment for Auditory Sensorimotor Gaiting in Two Rodent Models of Schizophrenia
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Introduction
Schizophrenia is a neurological disorder found in approximately 1% of the population. A common hallmark of schizophrenia is an increase in dopamine D2 receptor sensitivity. Individuals with schizophrenia have increased neuroinflammation with microglial activation in their prefrontal cortex and hippocampus. Increased levels of the pro-inflammatory cytokine tumor necrosis-factor-alpha (TNF) are associated with psychotic symptoms. Rats that receive quinpirole, a dopamine D2-like agonist, during the neonatal period display an increase in sensitivity of the D2 receptor without an increase in D2 receptor number throughout the animal’s lifetime, which mimics increases in dopamine D2 receptor sensitivity during schizophrenia. Polynosinic-polycytidylic acid (Poly I:C) given during the rat neonatal period (postnatal days 5-7) mimics an increased immune response during early brain development (equivalent to 2nd trimester in humans), which increases the prevalence of schizophrenia.

Individuals diagnosed with schizophrenia demonstrate deficits in prepulse inhibition (PPI), a behavioral measure of auditory sensorimotor gating. Newly developed anti-neuroinflammatory, PD2024 (P2D Bioscience, Cincinnati, OH), reduces TNF action in vitro and in vivo.

Purpose & Hypotheses of the Present Study
The purpose of this study was to determine:
1. Does administration of PD2024 alleviate PPI deficits known to exist in the neonatal quinpirole rat model throughout development?
2. Does administration of PD2024 alleviate PPI deficits known to exist in the Poly I:C rat model throughout development?

Hypotheses:
1. Treatment with PD2024 will result in alleviation of PPI deficits in the NS rat model in adolescence and adulthood.
2. Treatment with PD2024 will result in alleviation of PPI deficits in the Poly I:C rat model in adolescence and adulthood.

Methods
Neonatal Quinpirole Model
• Rats were the male offspring of six pregnant dams, and day of birth was counted as postnatal day (P0).
• One male from each litter was assigned to each drug treatment group to control for within litter variance.
• Beginning on P1, all animals were IP administered quinpirole HCl (Sigma-Aldrich, St. Louis, MO) (1 mg/kg) or saline once daily throughout the animal’s lifetime, which mimics increases in dopamine D2 receptor sensitivity during schizophrenia.
• Polynosinic-polycytidylic acid (Poly I:C) given during the rat neonatal period (postnatal days 5-7) mimics an increased immune response during early brain development (equivalent to 2nd trimester in humans), which increases the prevalence of schizophrenia.

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Results

Dietary Treatment
• Both models were given regular (control) chow or PD2024 orally (10mg/kg) from P30-65 in their diet.

Model Acronym Descriptions
• There were a total of 4 conditions for each rat model.
• The NS model: NS-PD2024, NS-NS, NS-Saline-Control, NS-Control
• The first acronym represents neonatal drug treatment (NS-Neonatal Saline; NO-Neonatal Quinpirole) and the second acronym represents which diet the group received beginning on P30.
• The Poly I:C model: Poly I:C-Control, Poly I:C-PD2024, Saline-Control, Saline-PD2024.

Prepulse Inhibition Testing (PPI)
• Animals were placed into a glass-steel dome (height = 6 cm) that was attached to a platform (11 cm wide x 15 cm long) mounted on a stainless steel ellipse in a sound attenuating chamber (28 cm tall x 30 cm wide x 36 cm in depth).
• Rats were administered three different trial types semi-randomly assigned, which included pulse trials, prepulse trials, and no stimulus trials, with randomized inter-trial intervals (ITIs) between each trial.
• On each daily session, the rats were placed into the dome and given a 5 min habituation period with only the background noise (70 dB white noise) presented.
• A prepulse trial was a 120 dB startle pulse administered that was not preceded by a prepulse.
• A no stimulus trial was a trial in which no stimulus was given.
• The start behavioral response was recorded within a 250 millisecond window after the stimulus was presented, and was measured in Newtons.
• All animals were given a randomized presentation of 25 trials which included 5 no stimulus, 15 prepulse trials (5 trials of each prepulse auditory level: 73, 76, and 82 dB) and 5 pulse trials.
• In both models, animals were PPI testing in mid-adolescence (P45/46) and in adulthood from P60-64.

Conclusions
• This study demonstrated that the administration of the anti-inflammatory PD2024 decreases PPI deficits in two different rat models of schizophrenia.

• In both models, administration of PD2024 led to an alleviation of PPI deficits regardless if animals were adolescents or adults.

• Improvement in PPI deficits in both models ranged between 15-30% in adolescence and adulthood.

• PD2024 treatment significantly reduced hippocampal microglial activation and TNF concentrations in the Poly I:C model.

• TNF is a viable target for the development of novel treatments for schizophrenia.

Funding provided by P2D Bioscience, Inc., Cincinnati, OH

Figure 1: PPI deficits in the neonatal quinpirole rat model
• A three-way ANOVA revealed a significant two-way interaction of neonatal drug treatment x diet F(1,32) = 16.72, p < .001.
• Across all prepulse dB intensities, Saline Control and Poly I:C PD2024 demonstrated significantly improved PPI performance compared to Poly I:C Control and Saline PD2024 groups.
• Saline Controls and the Poly I:C-PD2024 group were statistically equivalent across all decibel levels.

Figure 2: Adult Results.
• A three-way ANOVA revealed a significant interaction of neonatal drug treatment x diet F(1,32)=24.81, p<.01.
• Similar to the results in adulthood with the NS model, PD2024 alleviated PPI deficits produced by neonatal Poly I:C treatment.

• PD2024 treatment significantly reduced hippocampal microglial activation and TNF concentrations in the Poly I:C model.

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