INHIBITION OF TNF-ALPHA DECREASES MICROGLIA ACTIVATION IN RATS NEONATALLY TREATED WITH POLY I:C

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INHIBITION OF TNF-ALPHA DECREASES MICROGLIA ACTIVATION IN RATS NEONATALLY TREATED WITH POLY I:C

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Purpose & Hypotheses

The central aim of this study was to determine if treatment with an anti-inflammatory compound (PD2024 – TNFα modulator) can reduce microglial activation in rats neonatally treated with poly I:C.

Methods

Hypotheses:

1. Neonatal poly I:C treatment will result in increased microglial activation.
2. Neuroinflammation in the pFC and Hip as a result of neonatal poly I:C treatment will be attenuated by oral administration of PD2024.
3. Reduction in neuroinflammatory levels will be similar to control levels.

Results:

• Across all three brain areas, the Poly IC Control demonstrated increased microglia body fluorescence intensity (p<.05).
• Regardless of the brain area, rats administered PD2024 through the diet had decreased microglial activation levels similar to the saline controls.

Conclusions

• Treatment with Poly IC activates the neuroinflammatory response, indicated by elevated microglial levels.
• PD2024 is effective in reducing microglial activation through the oral administration of PD2024.
• PD2024 treatment was similar to the control group (Neonatal Saline/Control).
• TNFα modulation could reduce the dose-dependent side effects observed with current antipsychotic medications and moderate the neuroinflammation in those diagnosed with SCHZ.
• Future studies will examine additional TNFα modulators produced by collaborators at P2D Bioscience, Inc., Cincinnati, OH to determine efficacy across multiple compounds in the Poly IC model of schizophrenia.

Abstract

Introduction

Schizophrenia (SCHZ) is a chronic debilitating neurological and behavioral disorder that affects approximately 21 million people worldwide (1).

Current medical treatment options for the reduction of the dopamine D2 receptor, known to have supersensitivity in those diagnosed with SCHZ (2-4).

Treatment to modulate the receptor through the use of typical and atypical antipsychotics has a number of debilitating side-effect side effects, including motor extrapyramidal side effects, dyskinesia, akathisia, and tardive dyskinesia (2).

Increasing evidence suggests neuroinflammation in humans plays a significant pathophysiological role in SCHZ (5,6).

Individuals diagnosed with SCHZ have higher levels of inflammation in their CNS, particularly within specific brain regions, such as the prefrontal cortex (pFC) and hippocampus (Hip) (7).

Risk imparted with polyinosinic/polycytidylic acid (poly I:C) between postnatal days 5-7 show increased neuroinflammation during wean, consistent with SCHZ (8).

This study investigates the use of novel anti-inflammatory compounds produced by our collaborators at P2D Bioscience, Inc. (Children, OH) to reduce neuroinflammation via microglial cell quantification in rats neonatally treated with poly I:C.

Figure 2. Hippocampus IHC Analysis

Figure 3. Brain Area Cell Body Fluorescence

Figure 4. Summary Table

Figure 5. Confocal Microscope

Methods

Neonatal Poly IC Treatment (P5-7):

- All animals were fed food ad libitum.
- Animals in the Neonatal Poly IC/TNFα and Neonatal Saline/TNFα groups were given a single dose of TNFα on P10.
- Animals in the remaining two groups (Poly IC Control and Saline Control) were given a saline injection on P10.
- The two cohorts were identical up to P30 and did not contain any additional additions.

Analysis and Quantification

Poly IC Control and Poly IC/TNFα were compared statistically. All conditions.

Conclusions

- Treatment with Poly IC activates the neuroinflammatory response, indicated by elevated microglial levels.
- PD2024 is effective in reducing microglial activation through the oral administration of PD2024.
- PD2024 treatment was similar to the control group (Neonatal Saline/Control).
- TNFα modulation could reduce the dose-dependent side effects observed with current antipsychotic medications and moderate the neuroinflammation in those diagnosed with SCHZ.
- Future studies will examine additional TNFα modulators produced by collaborators at P2D Bioscience, Inc., Cincinnati, OH to determine efficacy across multiple compounds in the Poly IC model of schizophrenia.

References