Alcohol-Induced Neuroinflammation in an Animal Model of FASD and Neuroprotection by Anti-Inflammatory Agents

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LEARNING OBJECTIVES

• Understand the sensitivity of the developing brain to the toxic effects of alcohol
• Understand the role of alcohol-induced neuroinflammation in mediating toxicity in the brain
• Appreciate the potential of anti-inflammatory therapies in treatment of FASD
Microglial Activation

Occurs in Response to:
- Injury, infection, disease, toxins, ethanol

![Diagram showing stages of microglial activation]

Resting → Intermediate Activation → Fully Activated

Images of resting and activated microglia are shown.
Ethanol Impact on Neuron–Microglia Interactions

ETHANOL → ? → NEURON

harmful microglia → NEURON: NEURON DEATH, CNS DYSFUNCTION

beneficial microglia → NEURON: NEURON SURVIVAL, NORMAL CNS FUNCTION
Neonatal Mouse Model of 3\textsuperscript{rd} Trimester Fetal Alcohol Exposure

- Postnatal treatment (P4-9)
- E = ethanol treated
  - 3.5-4 mg/kg/day
  - BEC 200-325 mg/dl
- Control groups:
  - H = handled only
  - V = vehicle treated
Microglial Activation

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<th>HIPPOCAMPUS</th>
<th>CEREBELLUM</th>
<th>CEREBRAL CORTEX</th>
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<td>HANDLED CONTROL</td>
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<td>VEHICLE CONTROL</td>
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<td>ETHANOL</td>
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Neuroinflammatory Cytokine and Chemokine Expression

**HIPPOCAMPUS**
- **IL-1β**
- **TNF-α**
- **CCL2**

**CEREBELLUM**
- **IL-1β**
- **TNF-α**
- **CCL2**

**CEREBRAL CORTEX**
- **IL-1β**
- **TNF-α**
- **CCL2**
Potential Mechanisms of Ethanol-Induced Neuroinflammation in FASD Models
TLR-4 Signaling

ETHANOL

TLR-4

MYD88 PATHWAY

MYD88

TRIF PATHWAY

TRIF

INFLAMMASOMES

PRO-IL-1β → IL-1β

AP-1

NF-κB

IRF-3

CCL2

IL-1β

IL-6

TNF-α

IFN-β
MyD88-Dependent Signaling

IL-1β

Hippocampus

Wild type
MyD88 Knockout

Gene Expression

Cerebellum

Wild type
MyD88 Knockout

Gene Expression
Potential for Anti-Inflammatory Therapeutics in FASD
PPAR-γ Agonists

- Thiazolidinediones:
  Pioglitazone (Actos™)

- Docosahexanenoic acid (DHA): an ω-3 fatty acid
Pioglitazone: Prevention of Ethanol-Induced Microglial Activation: Quantitative Morphometry
Pioglitazone: Prevention of Neuroinflammatory Cytokine and Chemokine Expression

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<td><strong>IL-1β</strong></td>
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<td><img src="image2" alt="Graph" /></td>
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<td><strong>TNF-α</strong></td>
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<td><strong>CCL2</strong></td>
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Docosahexaenoic Acid (DHA): Prevention of Neuroinflammatory Cytokine Expression
Pioglitazone: Protection of Cerebellar Purkinje Neurons

VEHICLE  PIO

ETHANOL  PIO + ETHANOL

Purkinje Cell Number (x 10^3)

V  PIO  E  PIO + E

***  ***  ***
Summary

- Ethanol in the developing CNS activates the neuroimmune system
  - Microglial activation
  - Pro-inflammatory cytokine and chemokine expression
- Ethanol-induced neuroinflammation may occur through mechanisms including TLR-4 and downstream MyD88 and/or TRIF signaling
- PPAR-γ agonists – including DHA and pioglitazone – block neuroinflammation and prevent neurodegeneration in animal models of FASD
  - Suggests PPAR-γ agonists may be effective in treatment of FASD
Selected References


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NIH: National Institute on Alcohol Abuse and Alcoholism