Alcohol-Induced Neuroimmune Activity in the Developing Brain 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
FASD: Behavioral Consequences

- Primary cause of mental retardation
- Learning and memory deficits
- Executive function deficits
- Attention deficits
- Balance and motor coordination deficits
- Increased risk of addiction
FASD: Neuropathology

- Neuron apoptosis
- Inhibited neurogenesis
- Restricted neurotrophic support
- Impaired neuron migration
- Impaired dendrite arborization
- Impaired synaptogenesis
- Impaired synaptic plasticity
- Altered neurophysiology
FASD: Neuropathology

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- Altered neurophysiology
- **Neuroimmune system activation**
  - microglia are the principal neuroimmune cells
Microglial Activation

Response to:

- Homeostatic disruption
- Injury, infection, disease, toxins
Ethanol Impact on Neuron–Microglia Interactions

- **NEURON DEATH**
- **CNS DYSFUNCTION**

- **NEURON SURVIVAL**
- **NORMAL CNS FUNCTION**

**ETHANOL** → ?

- **harmful microglia**
- **beneficial microglia**

**NEURON**
Neonatal Mouse Model of 3rd Trimester Fetal Alcohol Exposure

- Postnatal treatment (P3-5 or P4-9)
- E = ethanol treated
  - 3.5 or 4 mg/kg/day
  - BEC 200-325 mg/dl
- Control groups:
  - H = handled only
  - V = vehicle treated
Microglial Activation

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Neuroinflammatory Cytokine and Chemokine Expression

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Potential Mechanisms of Ethanol-Induced Neuroinflammation in FASD Models
TLR-4 Signaling

ETHANOL

- MYD88 PATHWAY
  - MYD88
  - TRIF

- TRIF PATHWAY

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

Cerebellum

Gene Expression

Wild type  MyD88 Knockout

Wild type  MyD88 Knockout
CX3CL1 (Fractalkine) – CX3CR1 Signaling
Potential for Anti-Inflammatory Therapeutics in FASD
Peroxisome Proliferator Activated Receptor-γ (PPAR-γ) Agonist Protection in Neurodegenerative Disorders

- **Multiple Sclerosis**
  (Diab et al., 2002, J Immunol; Xu and Drew, 2007, J Immunol; Xu et al., 2009, J Leukocyte Biol; Solt et al., 2011, Nature)

- **Alzheimer’s Disease**
- **Spinal Cord Injury**
- **Stroke**
- **Parkinson’s Disease**
- **Amyotrophic Lateral Sclerosis**
- **FASD ... ?**
PPAR-γ Agonists

• Thiazolidinediones:
  Pioglitazone (Actos™)
  Rosiglitazone (Avandia™)

• Docosahexanenoic acid (DHA): an ω-3 fatty acid
## Pioglitazone: Prevention of Microglial Activation

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Pioglitazone: Prevention of Microglial Activation

- **Hippocampus**
- **Cerebellum**
- **Cerebral Cortex**
Microglial Activation: Quantitative Morphometry

**HIPPOCAMPUS**

**CEREBELLUM**

**CEREBRAL CORTEX**
Pioglitazone: Prevention of Neuroinflammatory Cytokine and Chemokine Expression

**IL-1β**

**TNF-α**

**CCL2**

**HIPPOCAMPUS**

**CEREBELLUM**

**CEREBRAL CORTEX**
Docosahexaenoic Acid (DHA): Prevention of Neuroinflammatory Cytokine and Chemokine Expression
Pioglitazone: Protection of Purkinje Neurons

VEHICLE

ETHANOL

PIO

PIO + ETHANOL

![Graph showing Purkinje Cell Number (x 10^3)]

- V
- PIO
- E
- PIO + E

*** indicates statistical significance at p < 0.001.
Summary

• Ethanol in the developing CNS activates the neuroimmune system
  – Microglial activation
  – Pro-inflammatory cytokine and chemokine expression

• Potential mechanisms of ethanol-induced neuroinflammation
  – TLR-4 and downstream MyD88 and/or TRIF signaling
  – Inflammasome signaling
  – Fractalkine signaling

• Ethanol-induced neuroinflammation in animal models of FASD occurs in brain regions linked to FASD behavioral deficits

• 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
Ongoing Studies

Determine:

• the mechanisms (TLR4, MyD88, TRIF, inflammasomes, fractalkine signaling pathways) by which ethanol induces neuroinflammation and neuropathology

• whether neuroinflammation contributes to long-term behavioral deficits associated with FASD

• whether PPAR-γ agonists and other anti-inflammatory molecules block ethanol-induced neuroinflammation, neuropathology, and behavioral deficits

These studies will:

• elucidate new therapeutic strategies

• provide proof-of-principle that anti-inflammatory agents including PPAR-γ agonists may be effective in treatment of FASD


Acknowledgements

Laboratory Contributors:

Gail Wagoner, LAT
J.C. Douglas, B.A., B.S.
Tonya Rafferty, B.S.
Jennifer Johnson, B.S.

Collaborator:

Kevin Phelan, Ph.D.

NIH: National Institute on Alcohol Abuse and Alcoholism
NIH: NIGMS IdeA Program/UAMS Center for Translational Neuroscience