Alcohol-Induced Neuroimmune Activity in the Developing Brain and Neuroprotection by Anti-Inflammatory Agents

Paul Drew, Ph.D. and Cindy Kane, Ph.D.

Department of Neurobiology and Developmental Sciences
University of Arkansas for Medical Sciences

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

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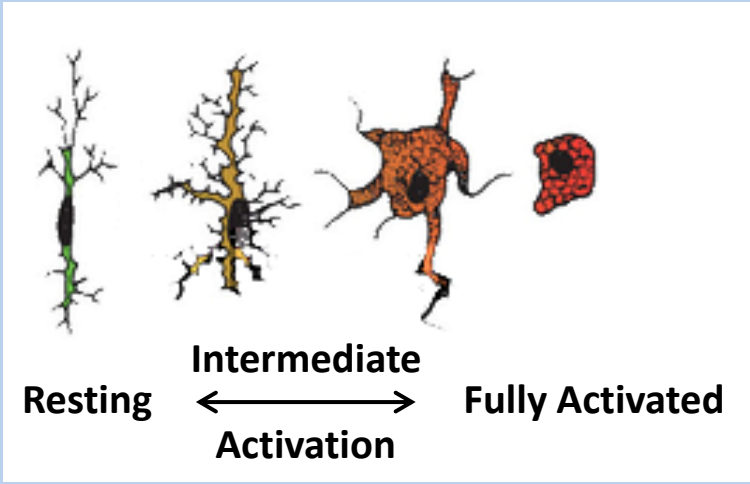
- Altered neurophysiology
- Neuroimmune system activation
  – microglia are the principal neuroimmune cells

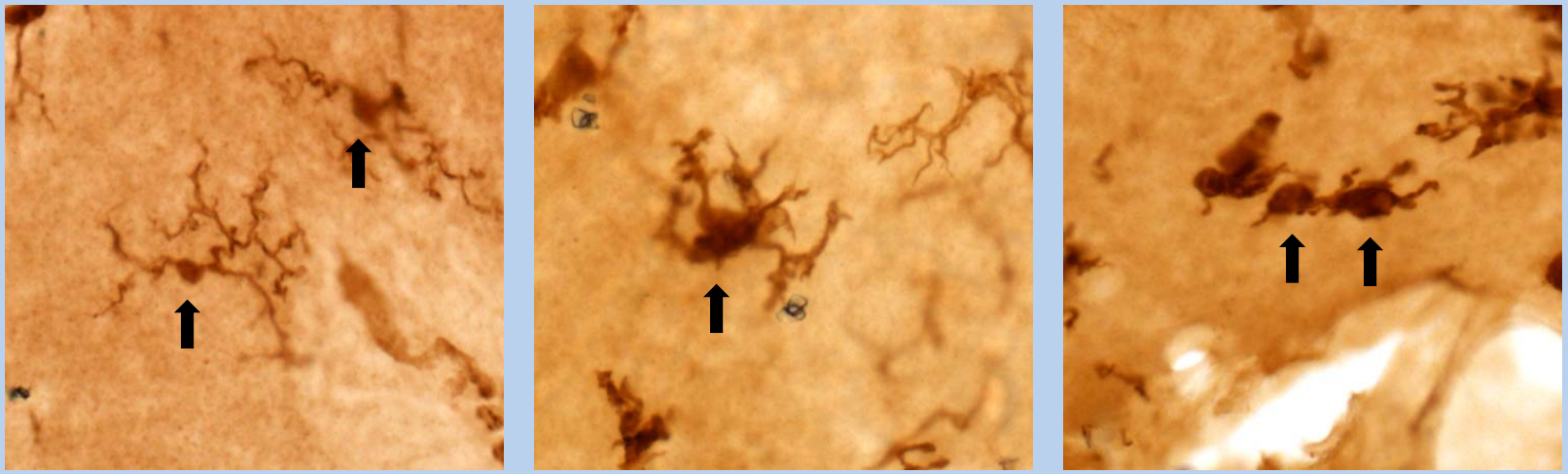
Microglial Activation

Response to:

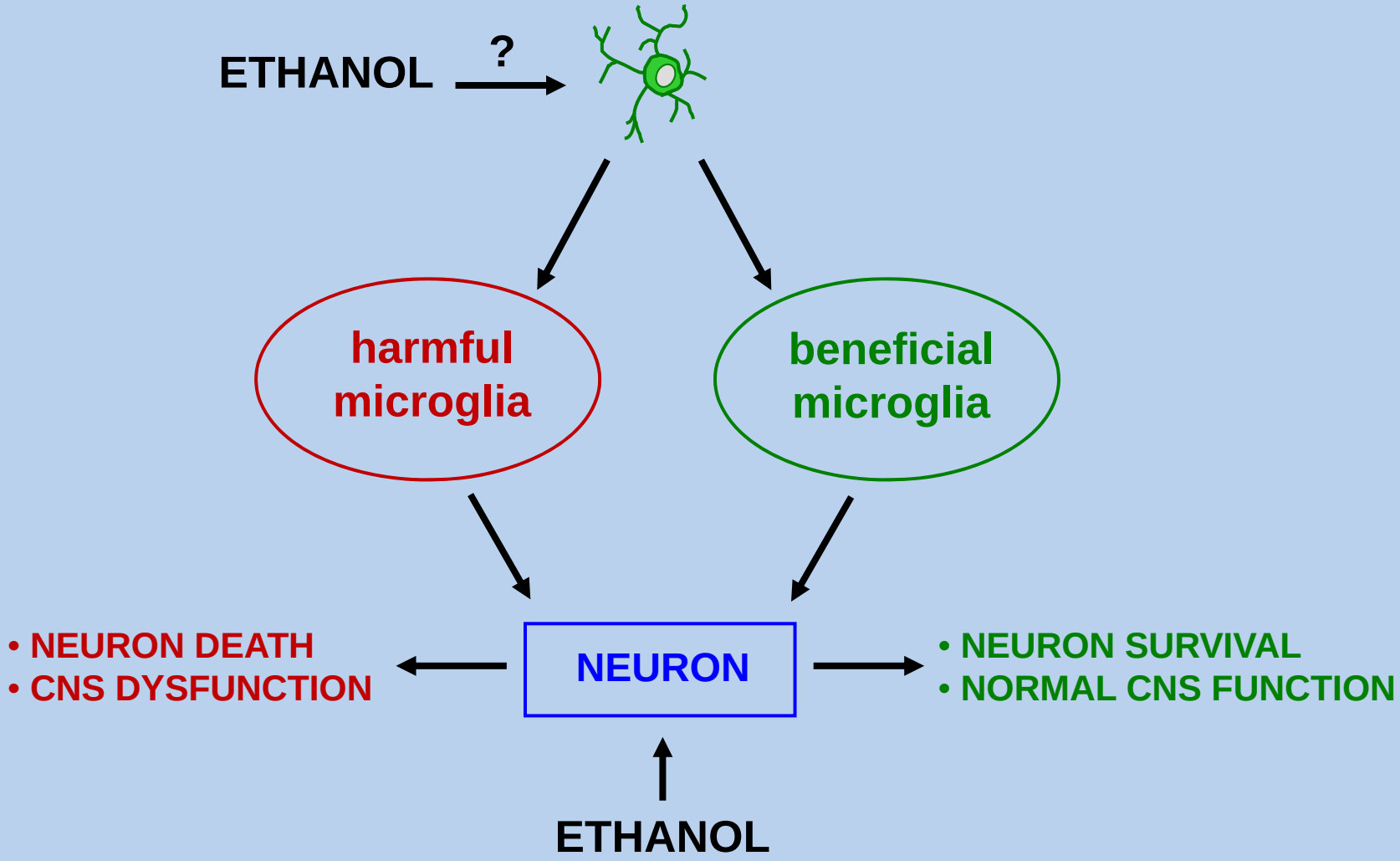
- Homeostatic disruption
- Injury, infection, disease, toxins



Resting **Activated**



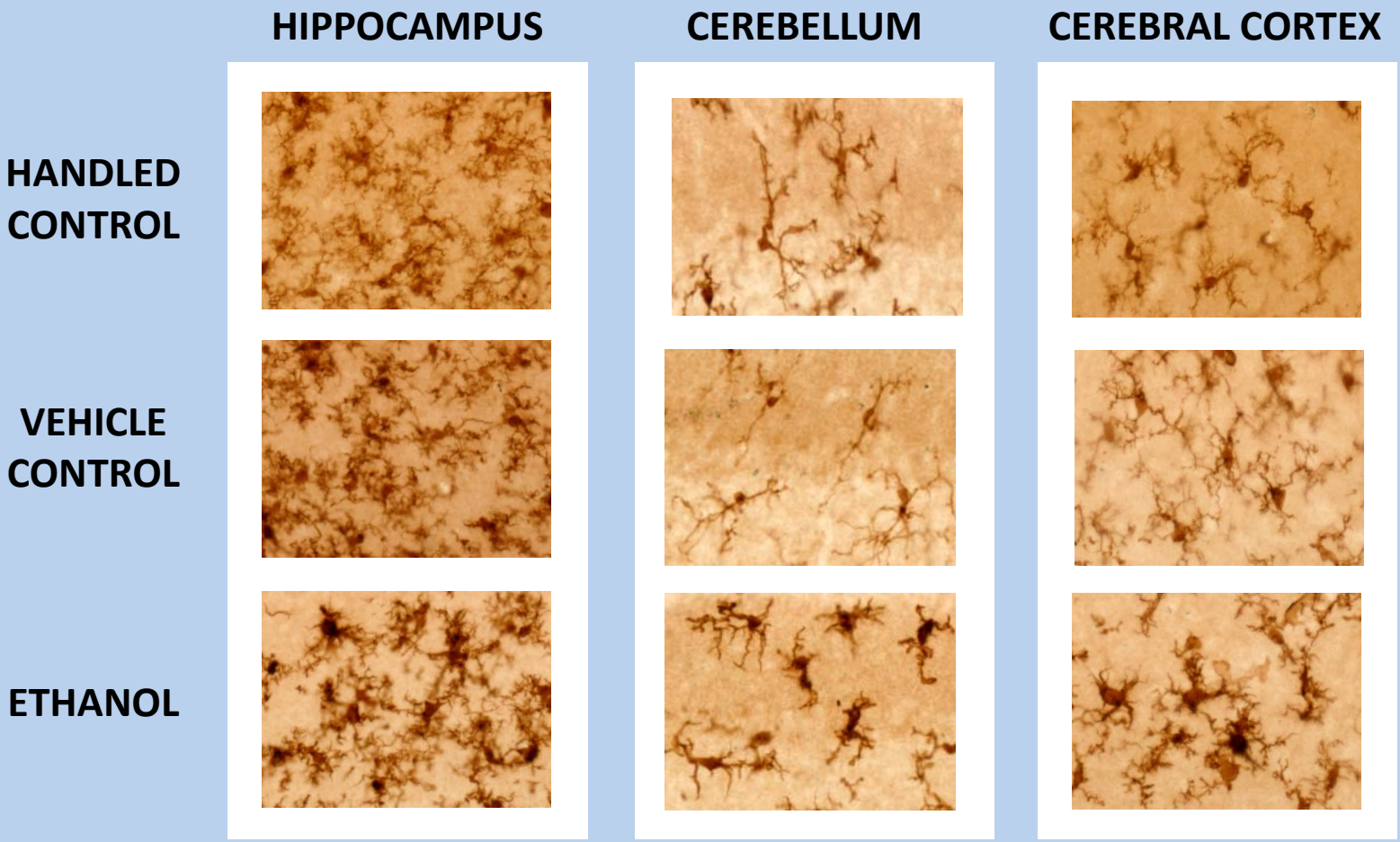
Ethanol Impact on Neuron–Microglia Interactions



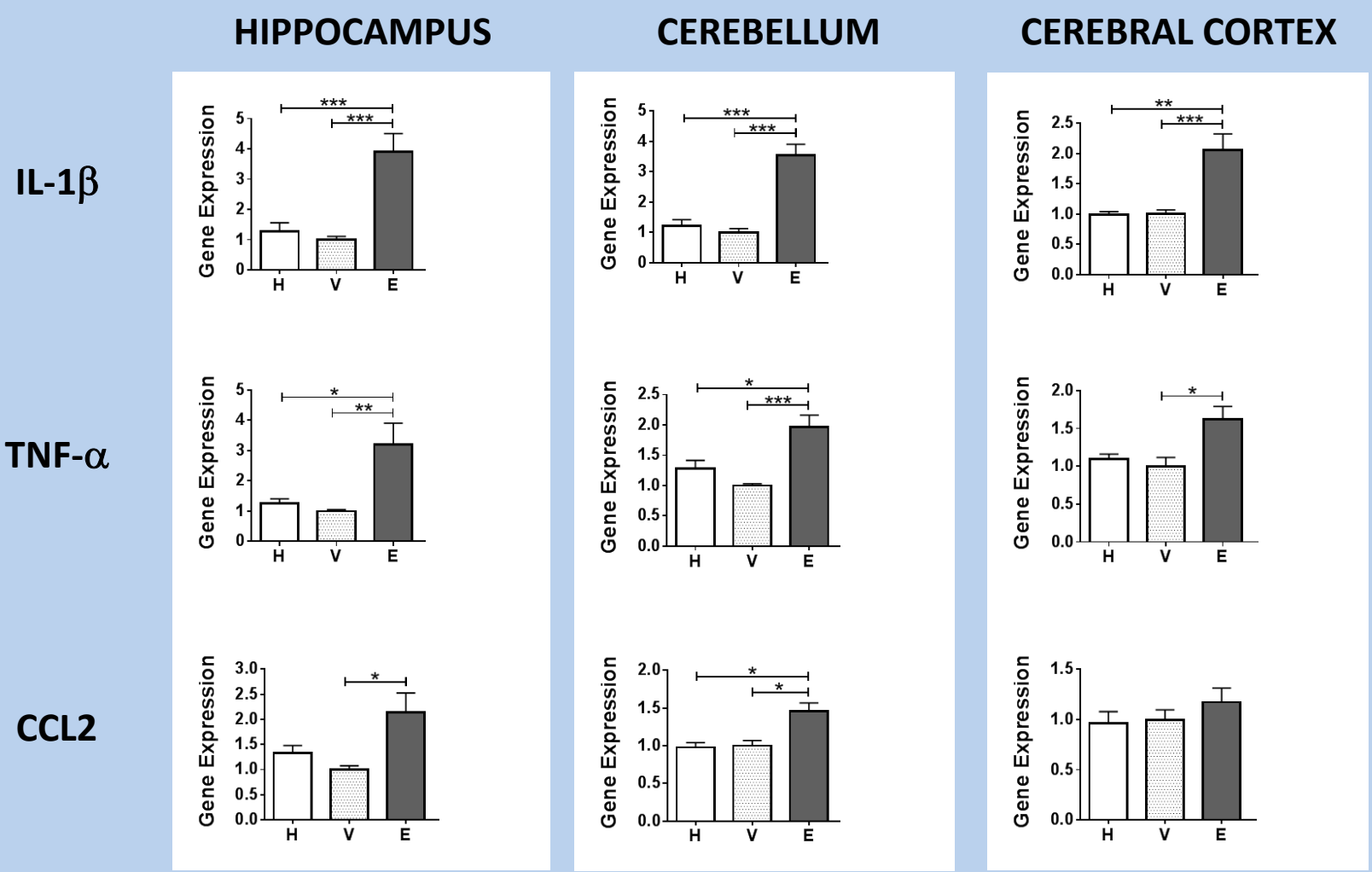
Neonatal Mouse Model of 3rd Trimester Fetal Alcohol Exposure

- 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

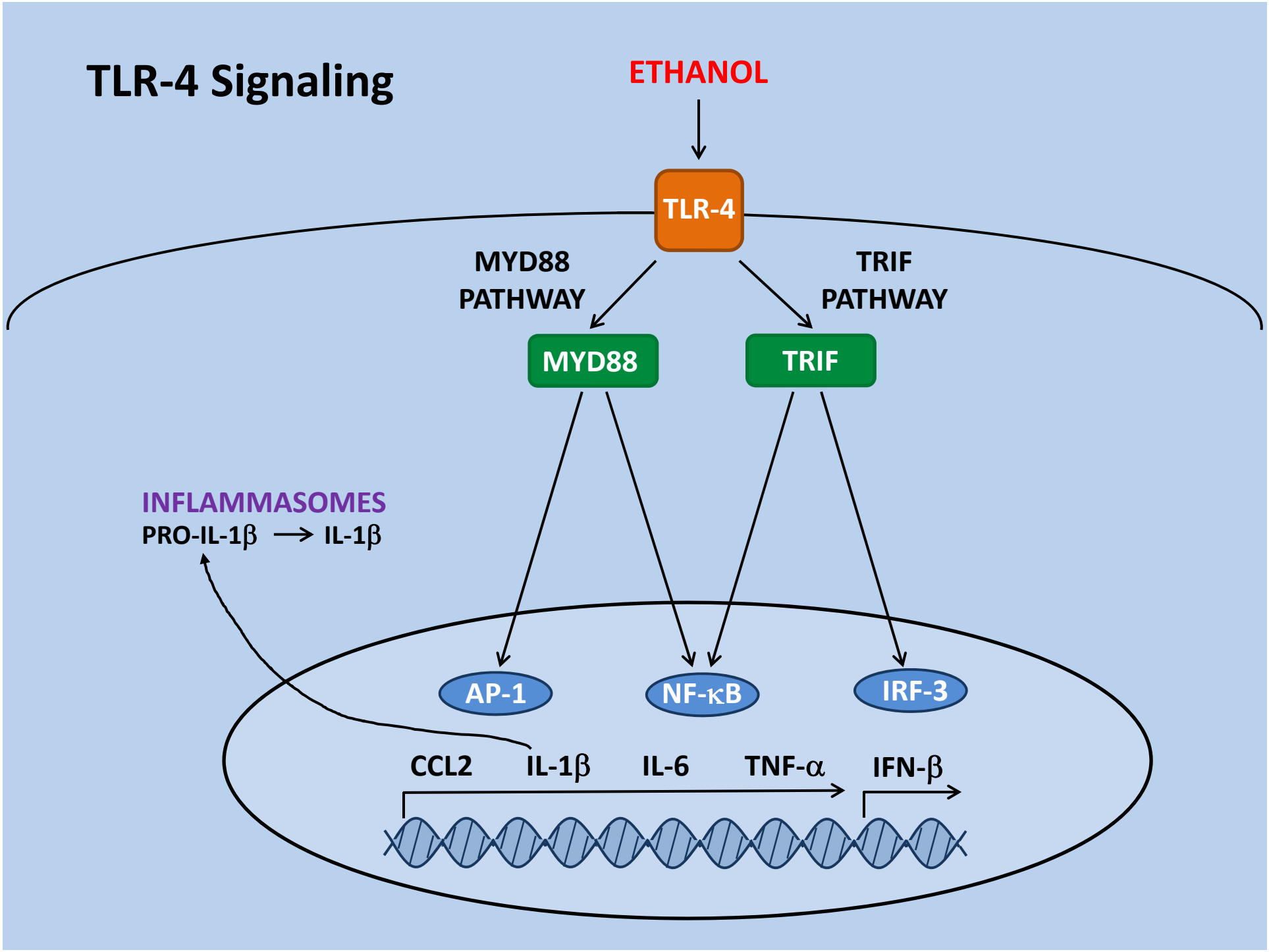
Microglial Activation



Neuroinflammatory Cytokine and Chemokine Expression



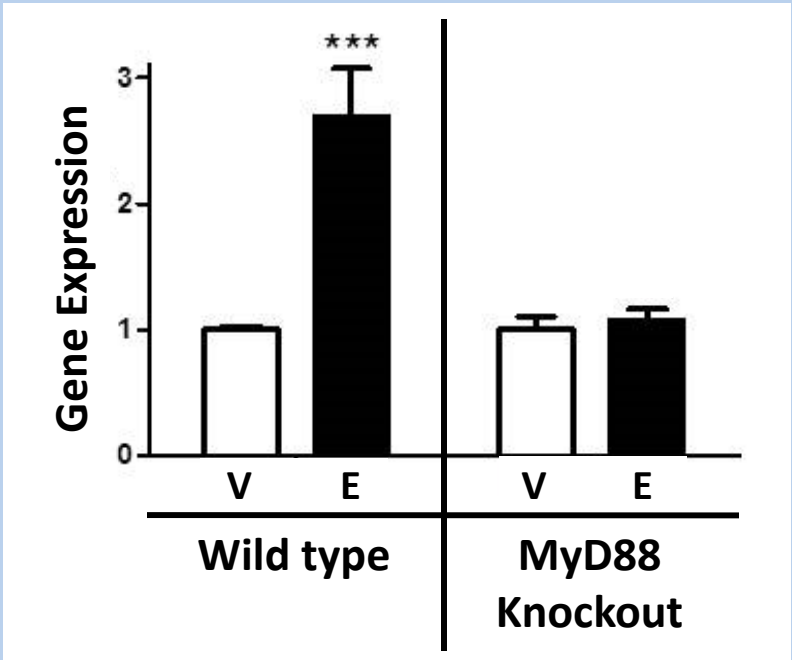
Potential Mechanisms of Ethanol-Induced Neuroinflammation in FASD Models


TLR-4 Signaling
ETHANOL
TLR-4
MYD88 PATHWAY
TRIF PATHWAY
MYD88
TRIF
INFLAMMASOMES
PRO-IL-1β → IL-1β
AP-1
NF-κB
IRF-3
CCL2
IL-1β
IL-6
TNF-α
IFN-β

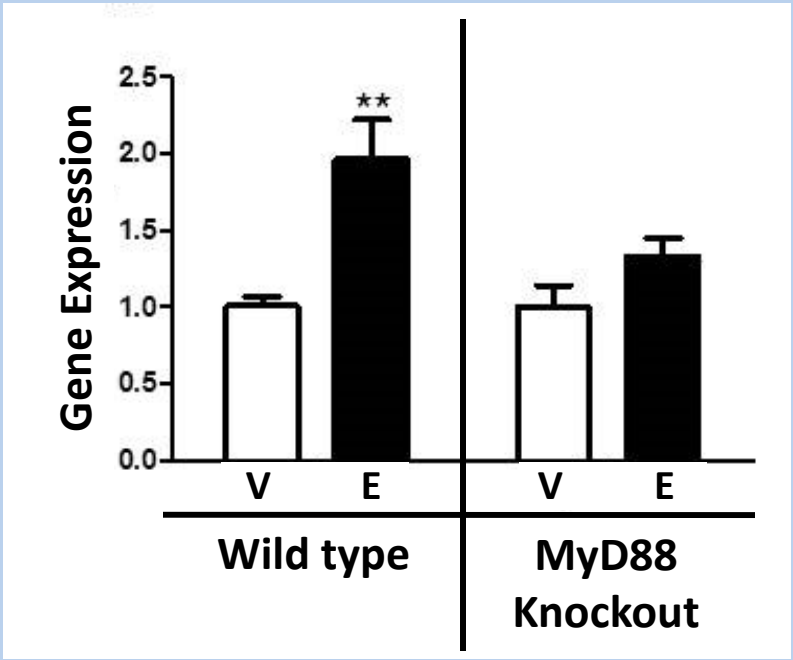
MyD88-Dependent Signaling

IL-1β

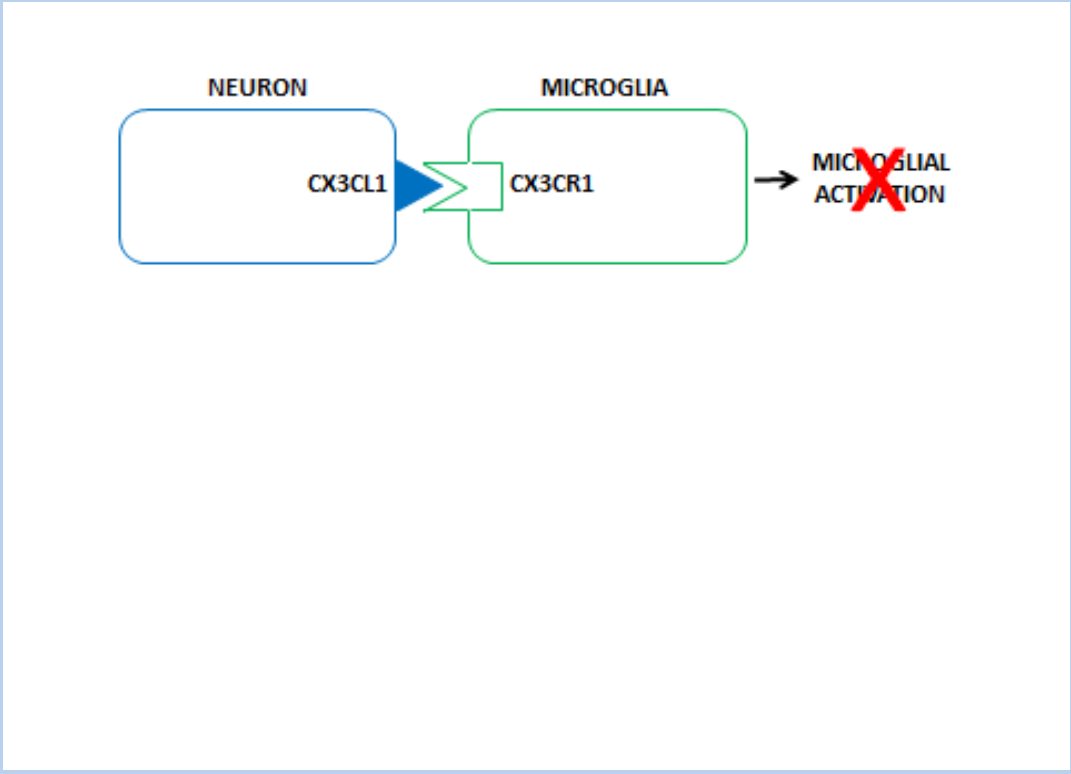
Hippocampus



Cerebellum



CX3CL1 (Fractalkine) – CX3CR1 Signaling



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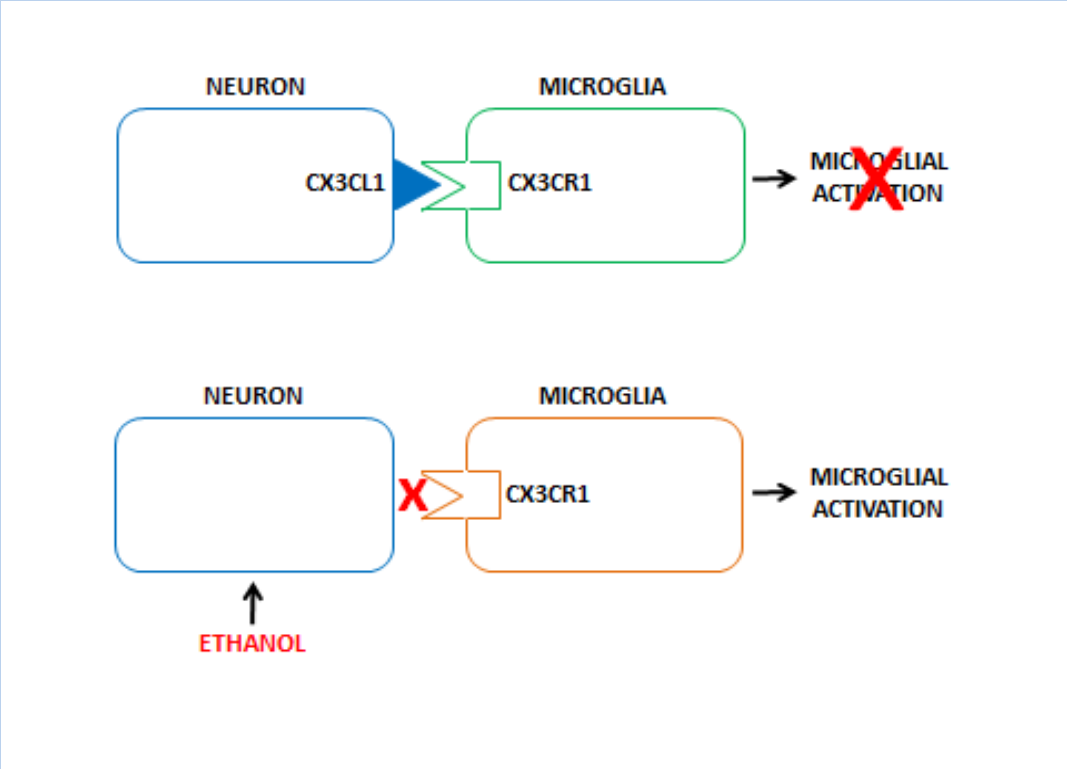
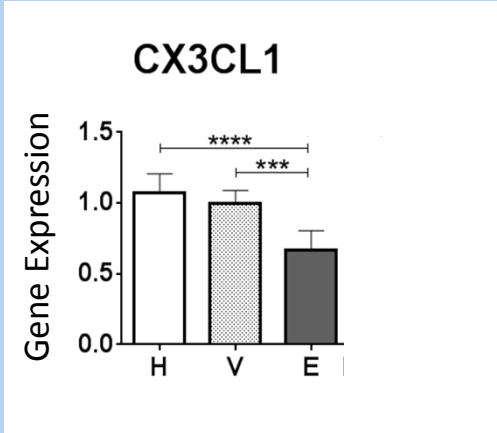




Potential for Anti-Inflammatory Therapeutics in FASD

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

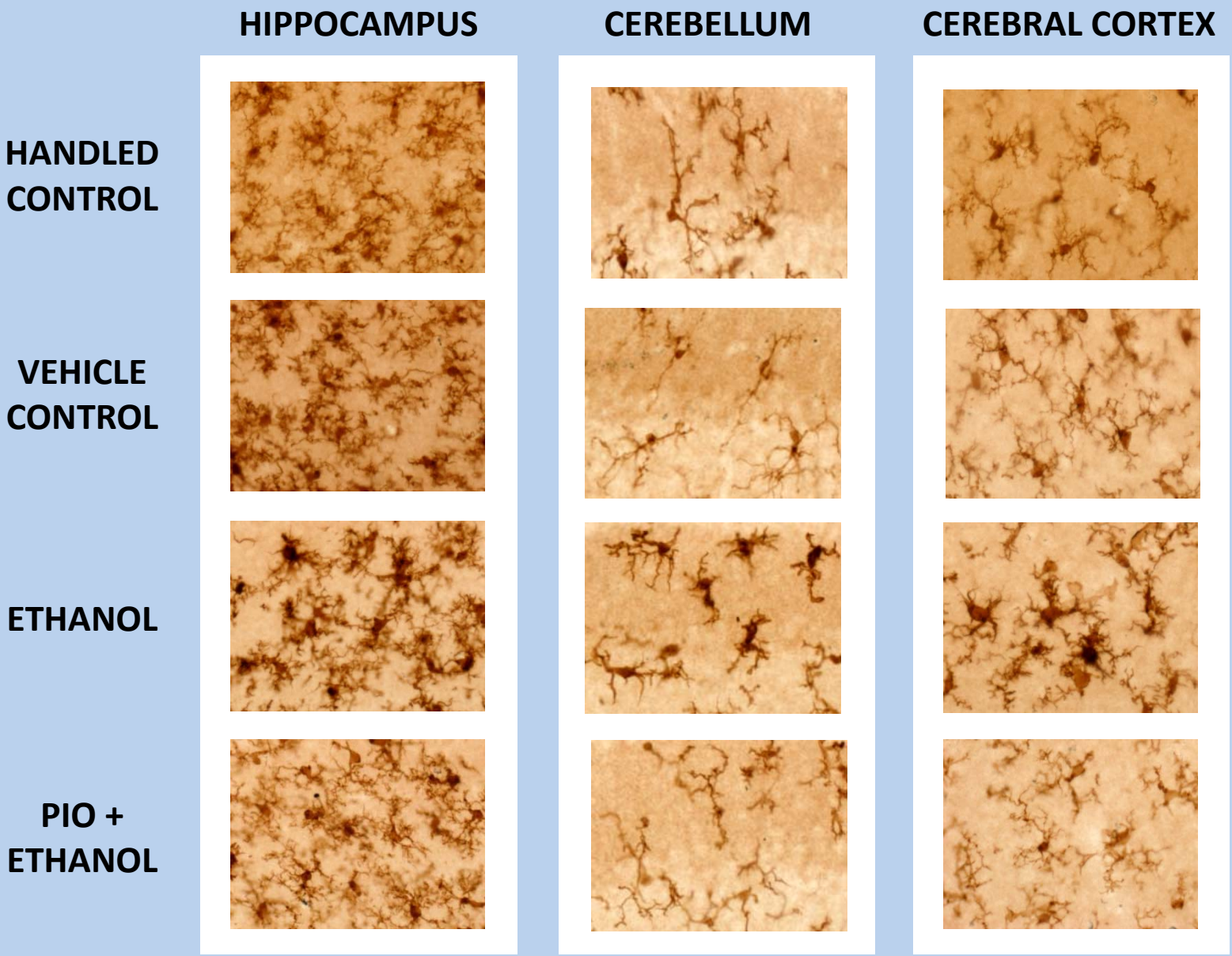
- **Thiazolidinediones:**

  Pioglitazone (Actos™)

  Rosiglitazone (Avandia™)

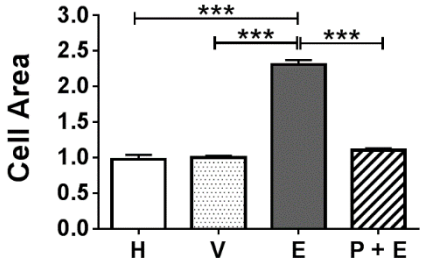
- **Docosahexanenoic acid (DHA): an ω-3 fatty acid**

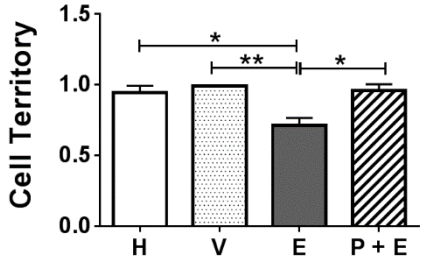
Pioglitazone: Prevention of Microglial Activation



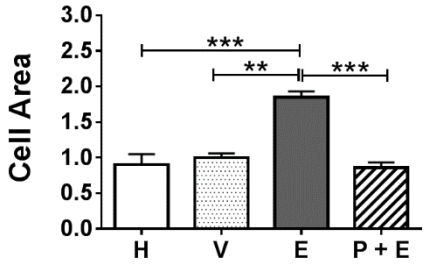
Microglial Activation: Quantitative Morphometry

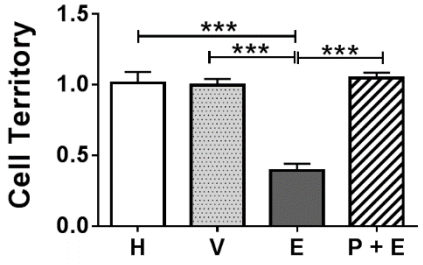
HIPPOCAMPUS



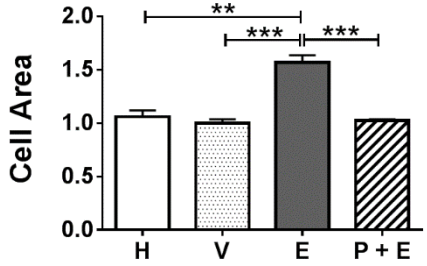


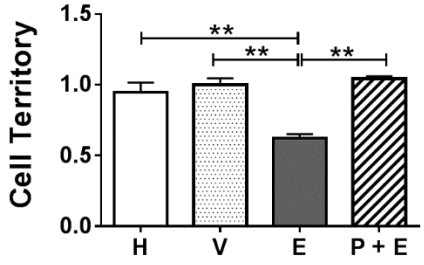
CEREBELLUM



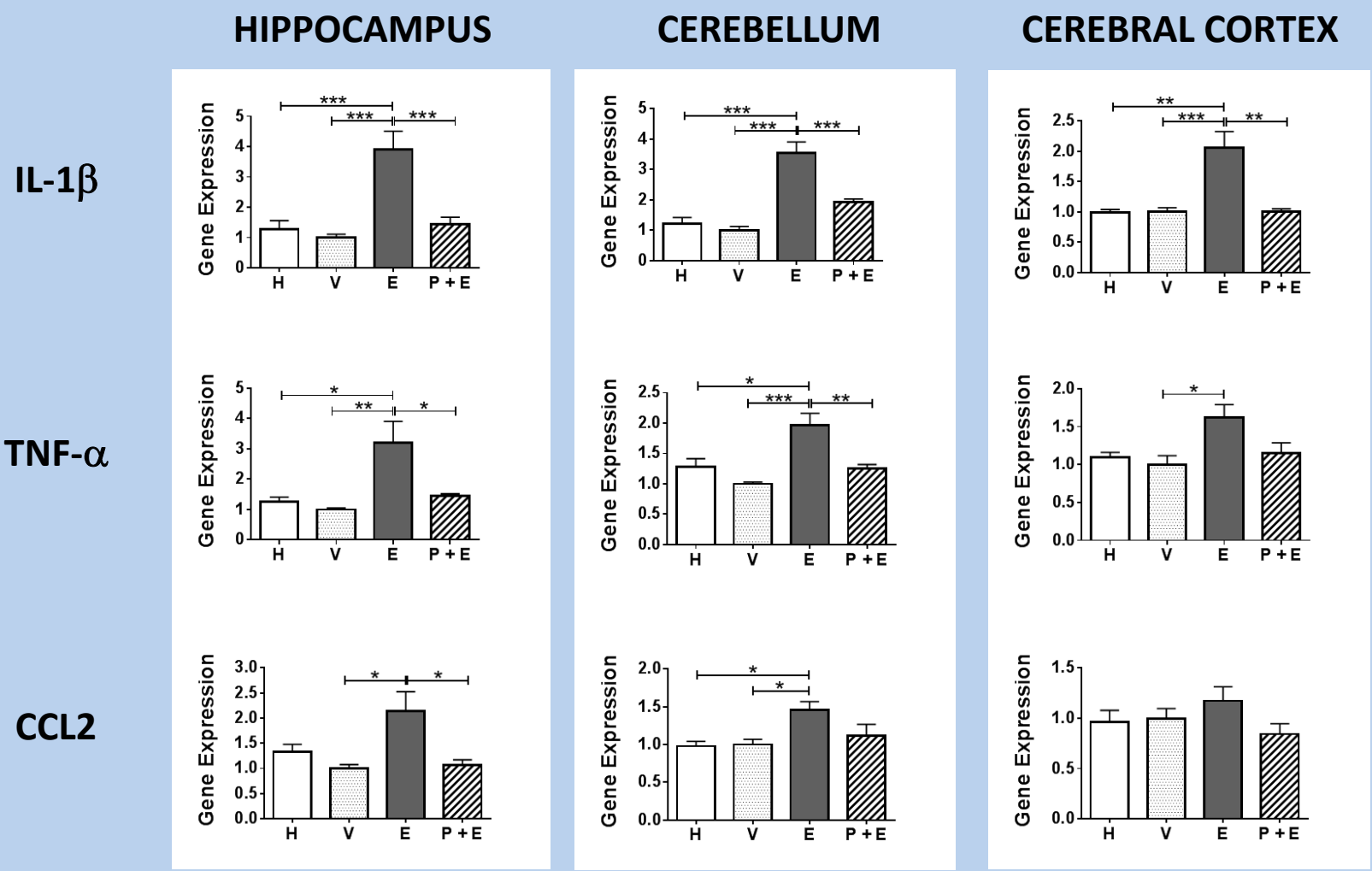


CEREBRAL CORTEX

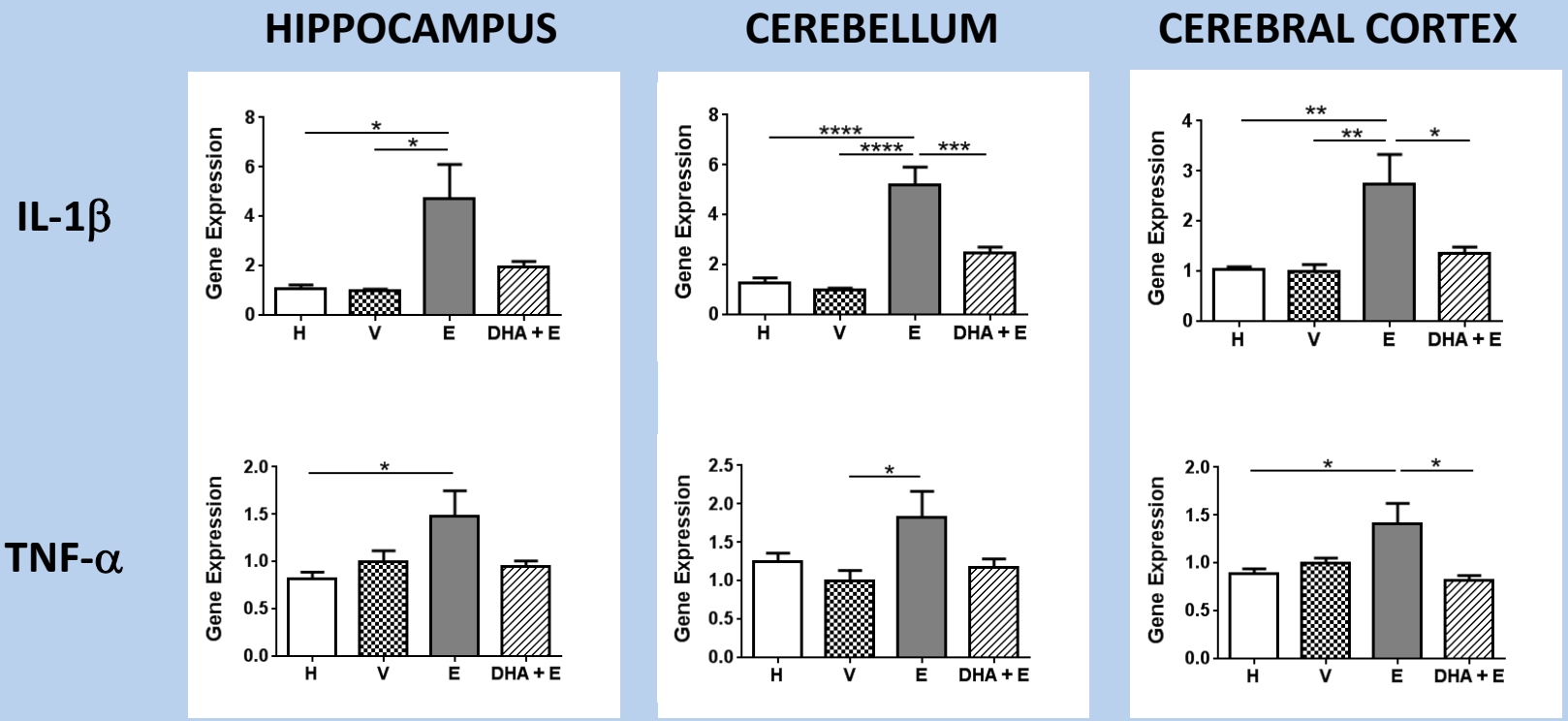




Pioglitazone: Prevention of Neuroinflammatory Cytokine and Chemokine Expression

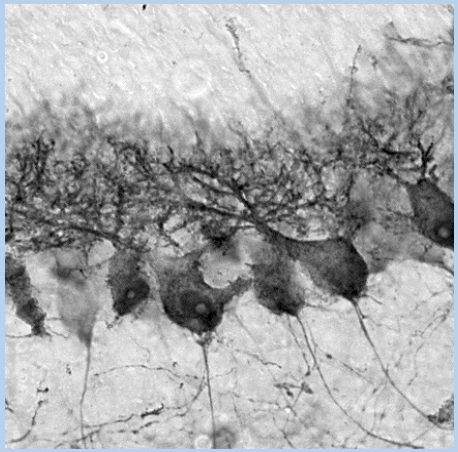


Docosahexaenoic Acid (DHA): Prevention of Neuroinflammatory Cytokine and Chemokine Expression

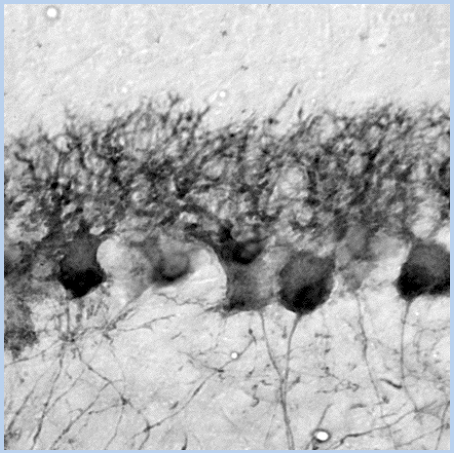


Pioglitazone: Protection of Purkinje Neurons

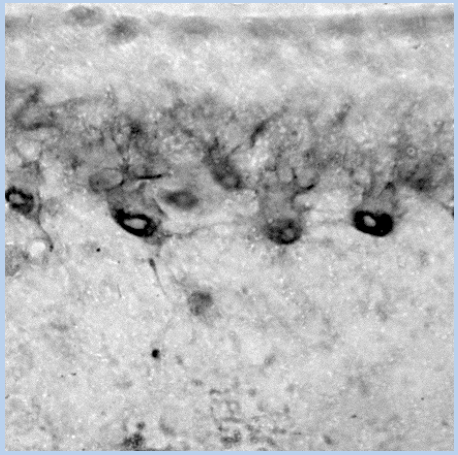
VEHICLE



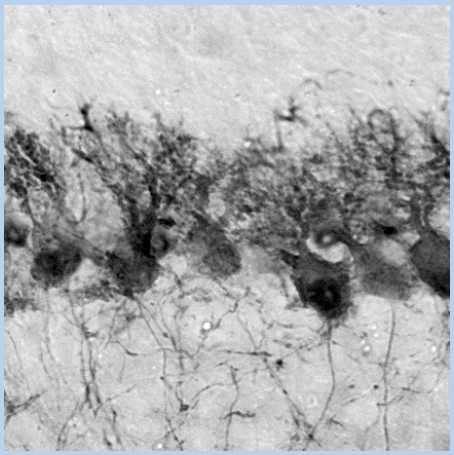
PIO

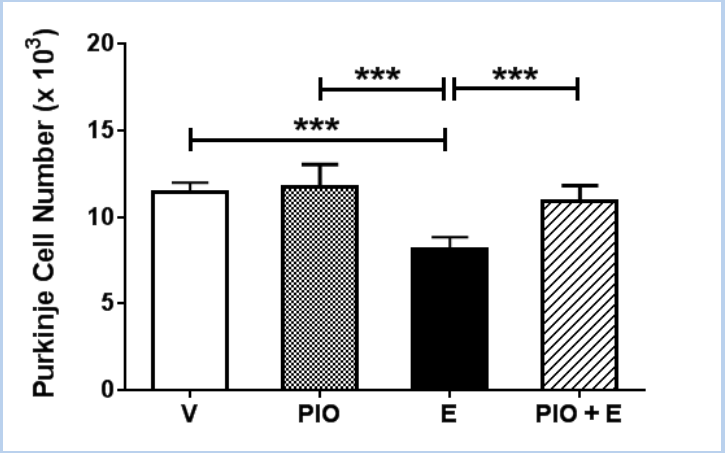


ETHANOL



PIO + ETHANOL





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

Selected References

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Acknowledgements

Laboratory Contributors:

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

Collaborator:

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