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

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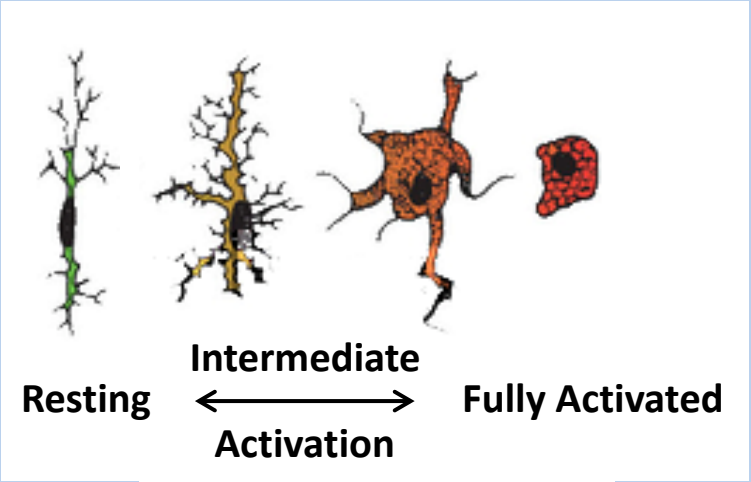
LEARNING OBJECTIVES

- 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

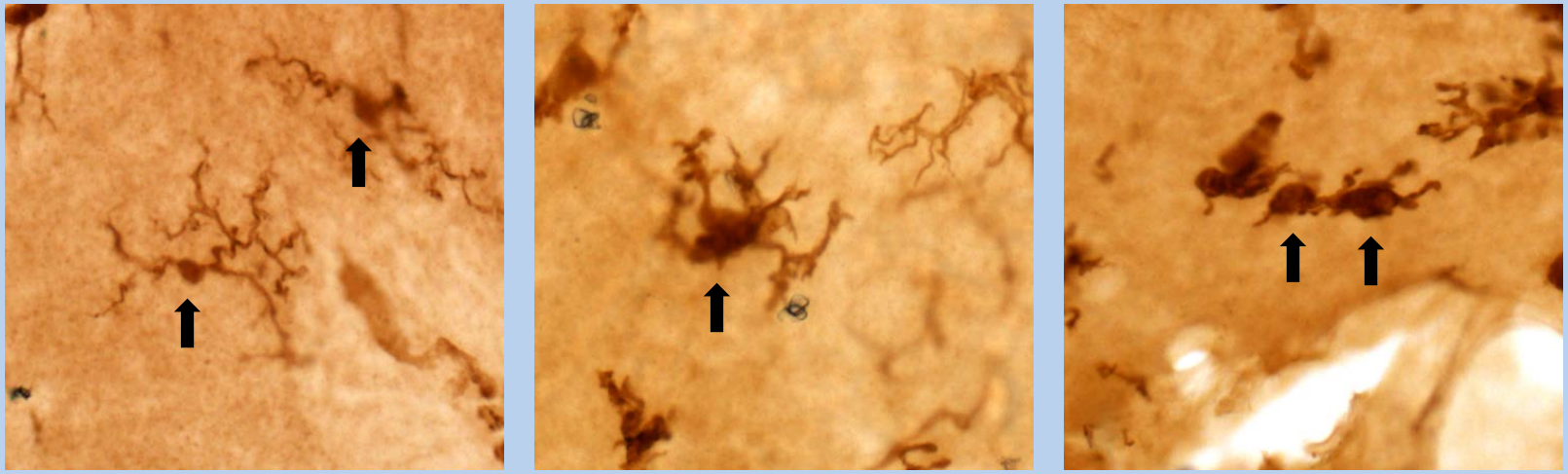
Microglial Activation

Occurs in Response to:

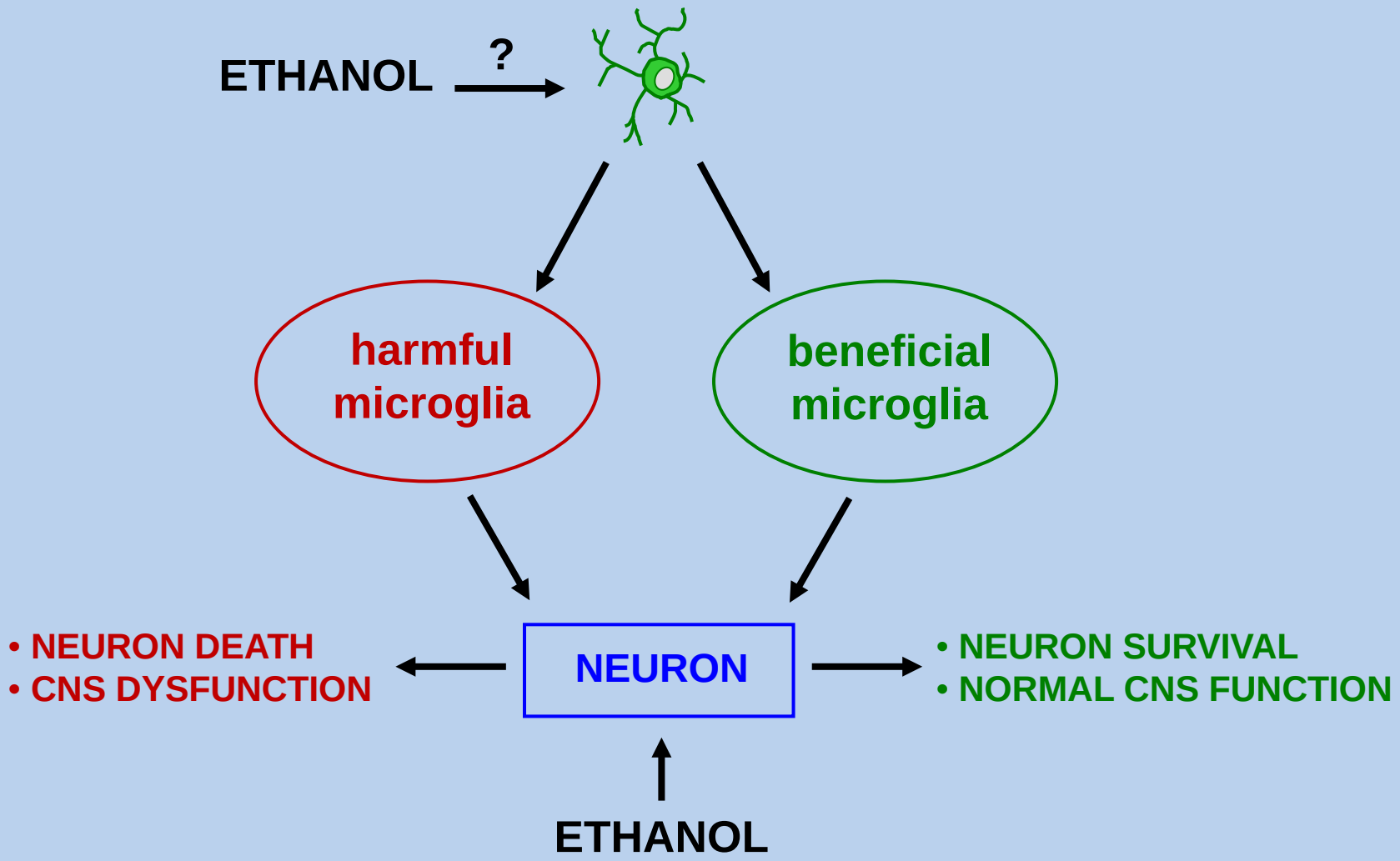
- Injury, infection, disease, toxins, ethanol



Resting **Activated**



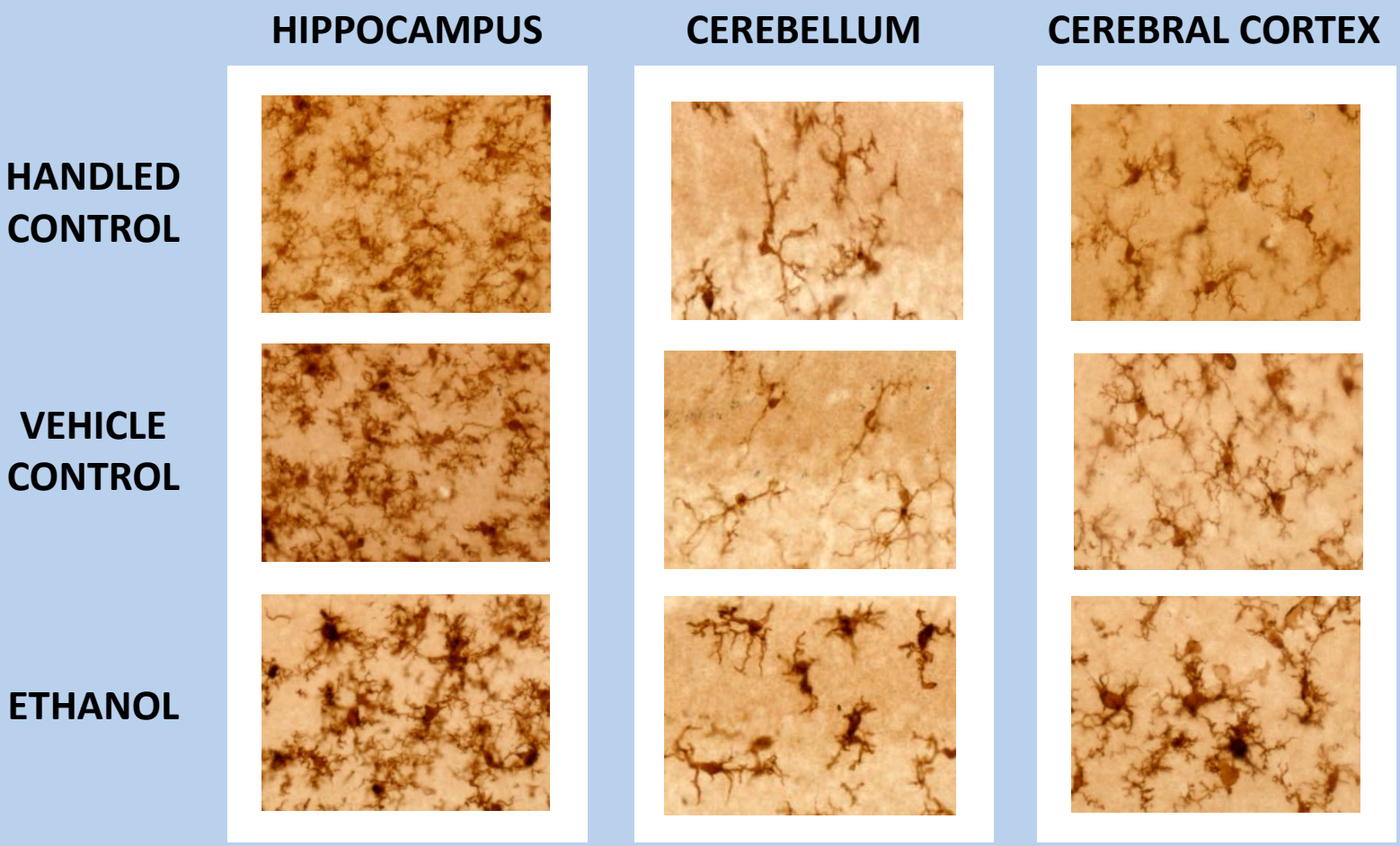
Ethanol Impact on Neuron–Microglia Interactions



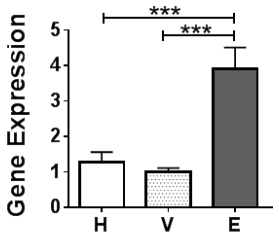
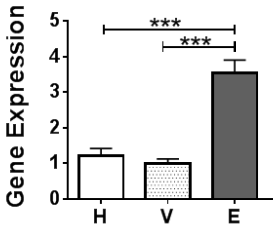
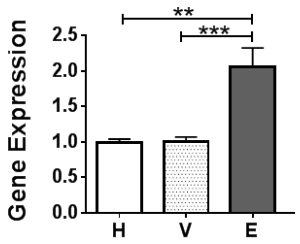
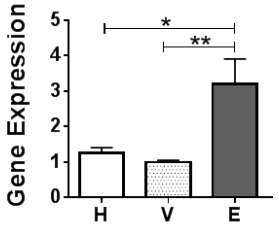
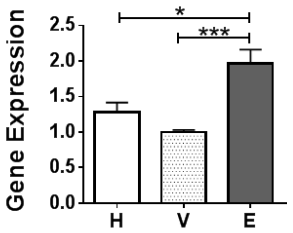
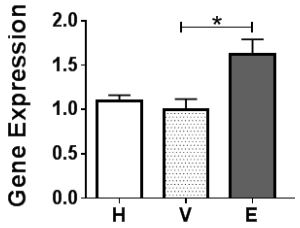
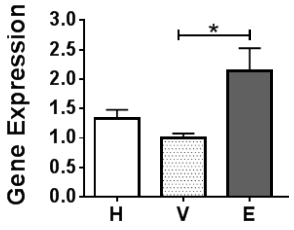
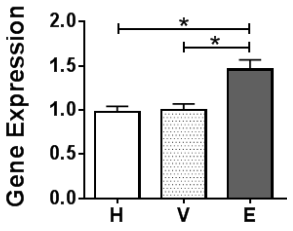
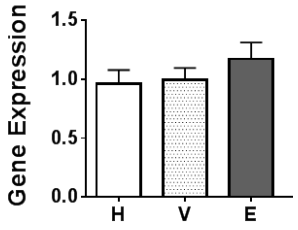
Neonatal Mouse Model of 3rd Trimester Fetal Alcohol Exposure

- 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

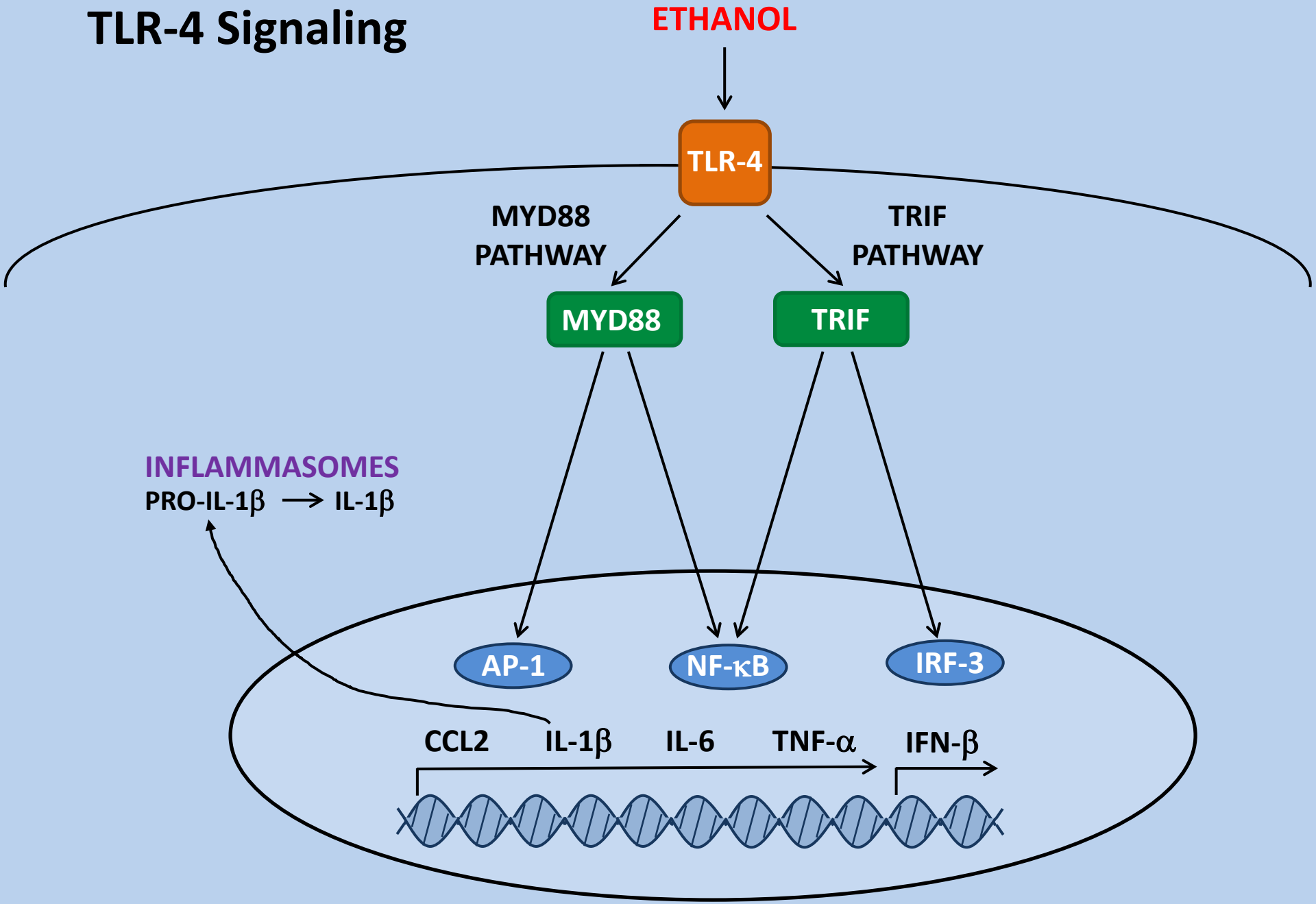


Neuroinflammatory Cytokine and Chemokine Expression

	HIPPOCAMPUS	CEREBELLUM	CEREBRAL CORTEX
IL-1β			
TNF-α			
CCL2			

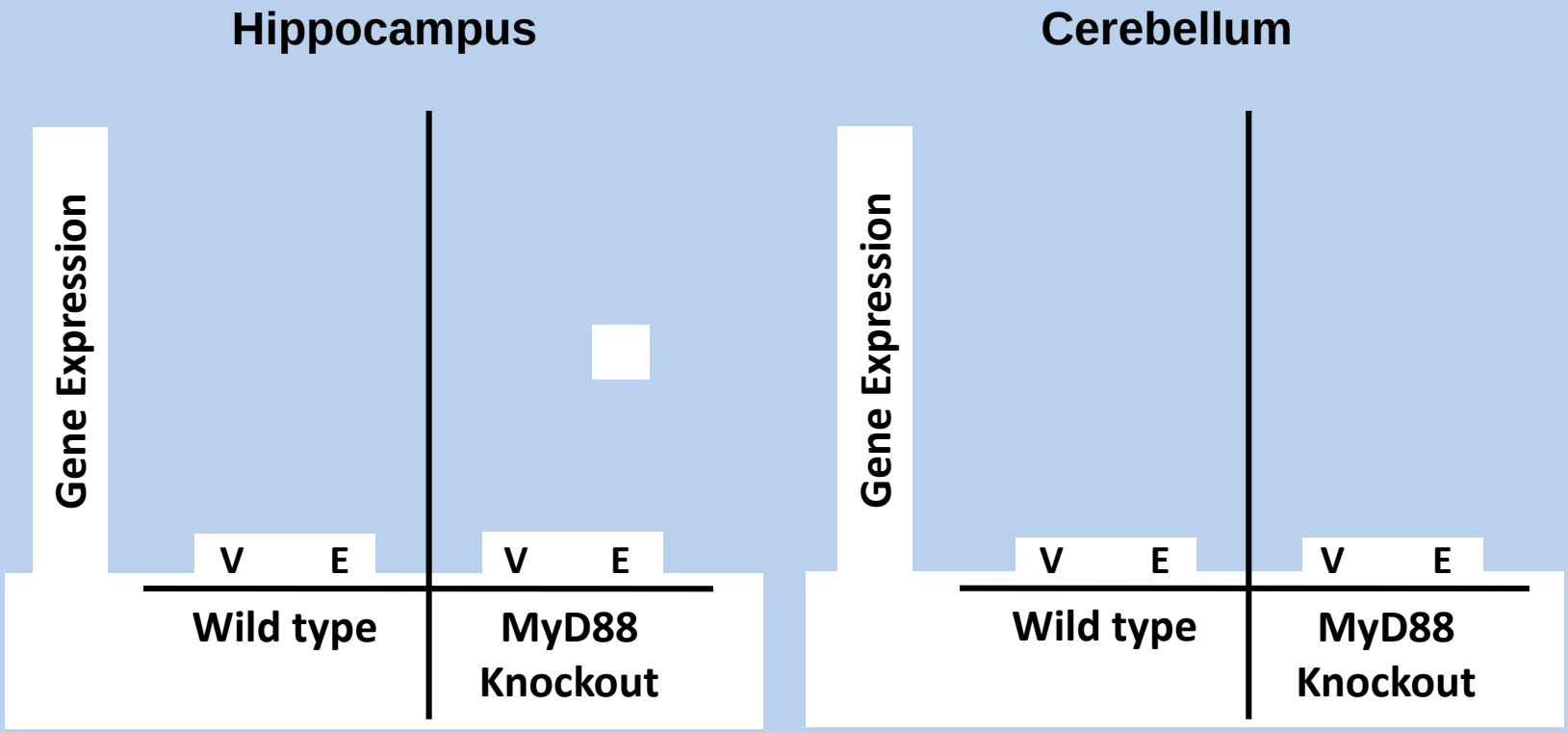
Potential Mechanisms of Ethanol-Induced Neuroinflammation in FASD Models

TLR-4 Signaling



MyD88-Dependent Signaling

IL-1β



Potential for Anti-Inflammatory Therapeutics in FASD

PPAR-γ Agonists

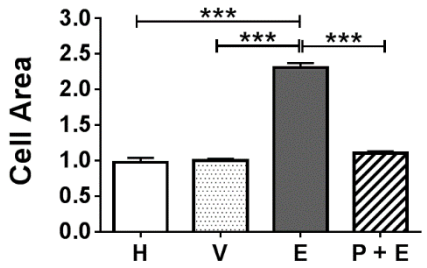
- **Thiazolidinediones:**

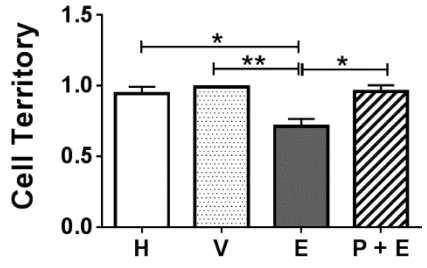
  Pioglitazone (Actos™)

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

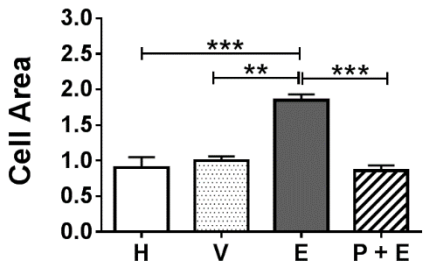
Pioglitazone: Prevention of Ethanol-Induced Microglial Activation: Quantitative Morphometry

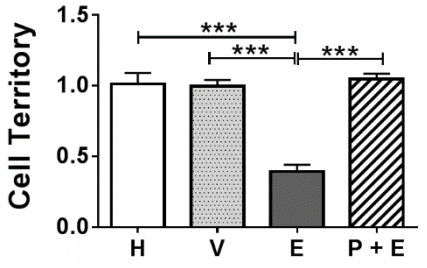
HIPPOCAMPUS



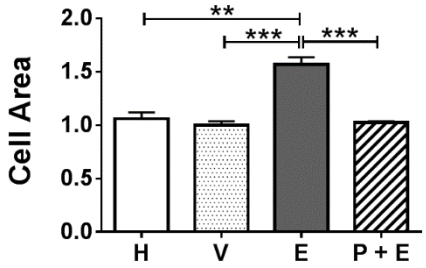


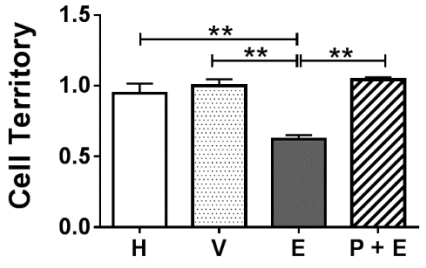
CEREBELLUM



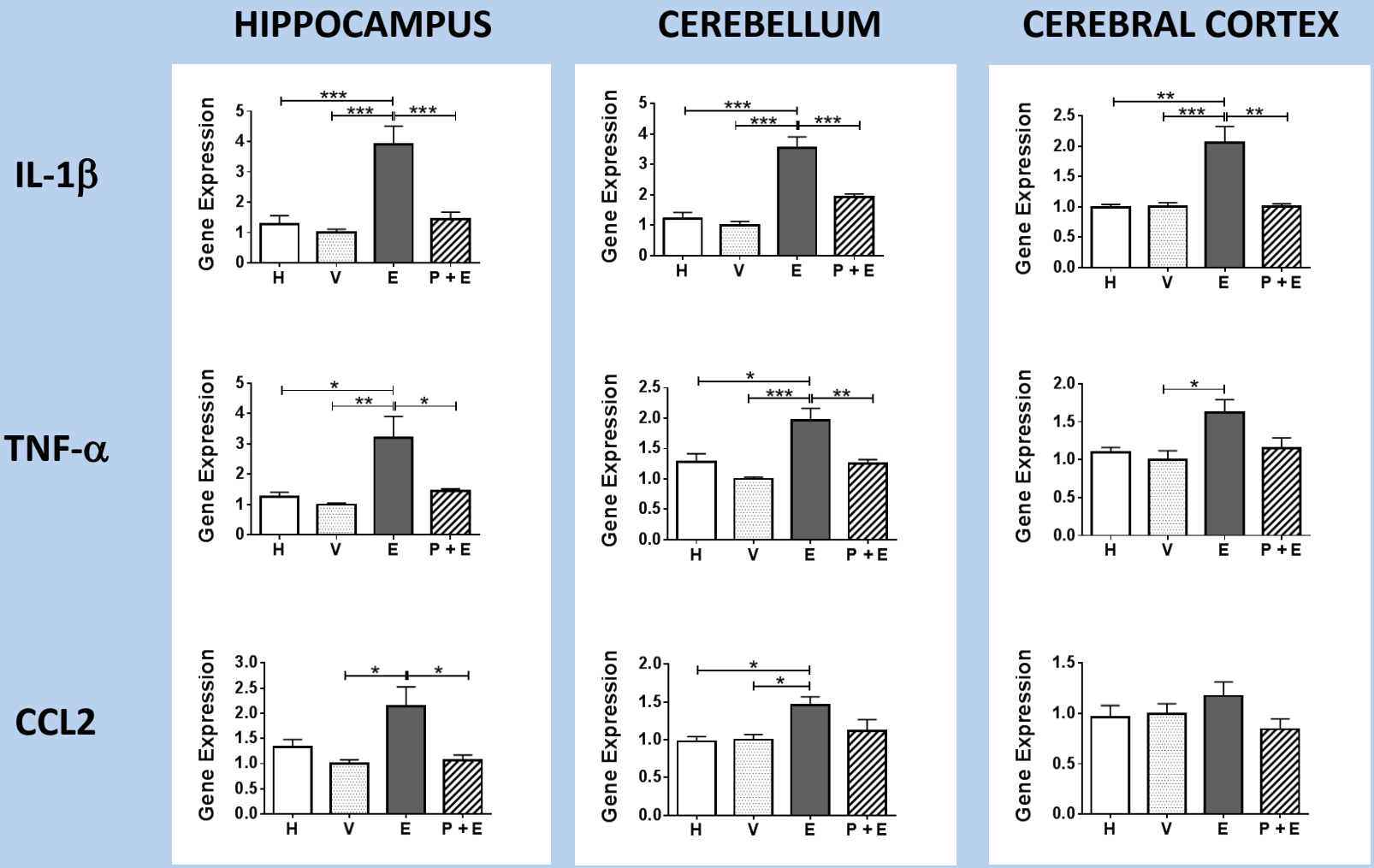


CEREBRAL CORTEX





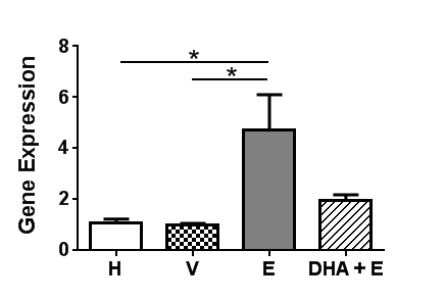
Pioglitazone: Prevention of Neuroinflammatory Cytokine and Chemokine Expression



Docosahexaenoic Acid (DHA): Prevention of Neuroinflammatory Cytokine Expression

IL-1β

HIPPOCAMPUS



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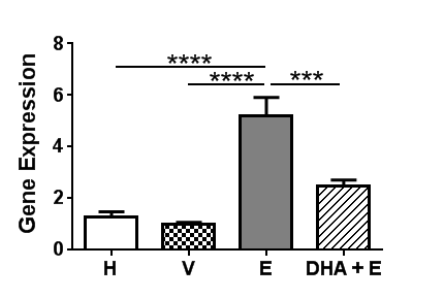
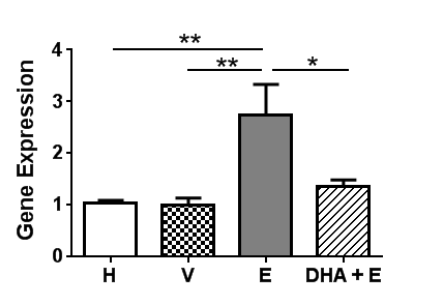
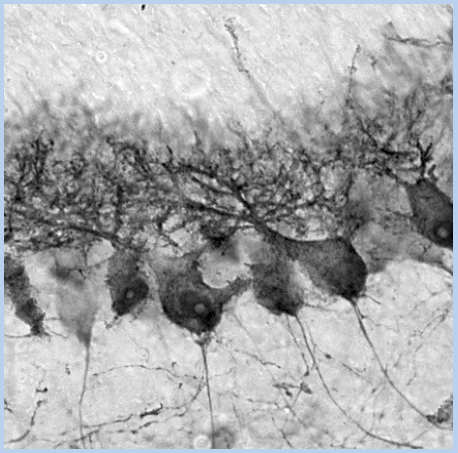


CEREBRAL CORTEX

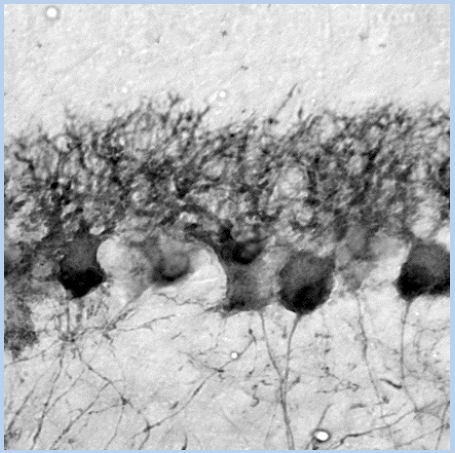


Pioglitazone: Protection of Cerebellar Purkinje Neurons

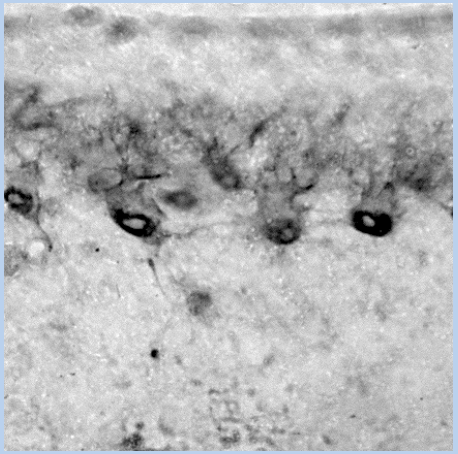
VEHICLE



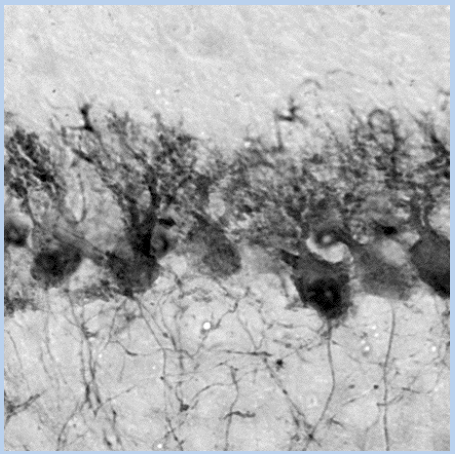
PIO

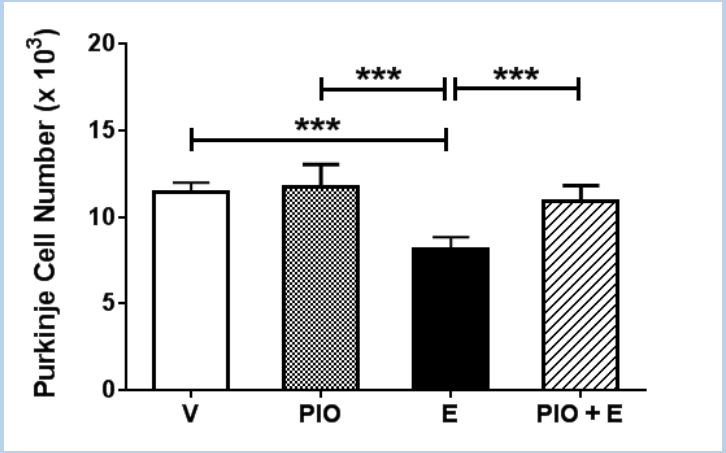


ETHANOL



PIO + ETHANOL





Summary

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

Kane, C.J.M., K.D. Phelan, L. Han, R.R. Smith, J. Xie, J.C. Douglas, and P.D. Drew. 2011. Protection of neurons and microglia against ethanol in a mouse model of fetal alcohol spectrum disorders by peroxisome proliferator activated receptor gamma ligands. Brain Behavior and Immunity. 25:S137-S145.

Kane, C.J.M., K.D. Phelan, J.C. Douglas, G. Wagoner, J. Walker-Johnson, J. Xu, and P.D. Drew. 2013. Effects of ethanol on immune response in the brain: region specific changes in aged mice. J. Neuroinflammation. 10:66-69.

Kane, C.J.M., K.D. Phelan, J.C. Douglas, G. Wagoner, J. Walker-Johnson, J. Xu, P.S. Phelan, and P.D. Drew. 2014. Effects of ethanol on immune response in the brain: region specific changes in adolescent versus adult mice. Alcohol Clin. Exp. Res. 38:384-391.

Drew, P.D., J.W. Johnson, J.C. Douglas, K.D. Phelan, and C.J.M. Kane. 2015. Pioglitazone Blocks Ethanol Induction of Microglial Activation and Immune Responses in the Hippocampus, Cerebellum, and Cerebral Cortex in a Mouse Model of Fetal Alcohol Spectrum Disorders. Alcohol Clin. Exp. Res. 39:445-454.

Kane, C.J.M., and P.D. Drew. 2016. Inflammatory Responses to Alcohol in the CNS: Nuclear Receptors as Potential Therapeutics for Alcohol-Induced Neuropathologies. Journal of Leukocyte Biology. 100:951-959.

Acknowledgements

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Gail Wagoner, LAT

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NIH: National Institute on Alcohol Abuse and Alcoholism