Rodent Models for Medication Development and their Application to Treat Fetal Alcohol Exposure

Susan Barron, Ph.D.

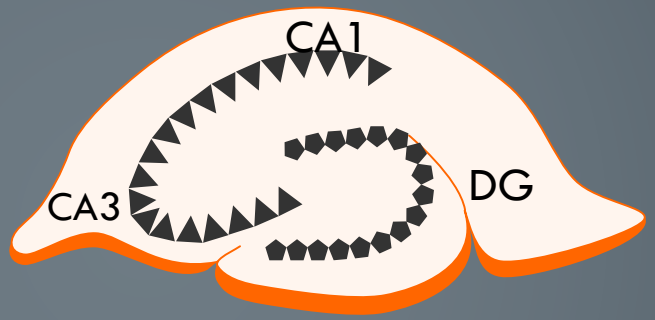
University of Kentucky

Learning objectives

- To learn about how pre-clinical models can be useful in the early stages of developing pharmacotherapies to eliminate or reduce fetal alcohol effects.
- To learn about some of the mechanisms by which alcohol affects the developing brain.
- To be able to discuss some of the possible real-life issues in developing medication for treating or reducing fetal alcohol effects in clinical populations.

Models we use to assess potential pharmacotherapies

- Organotypic hippocampal slice cell culture model



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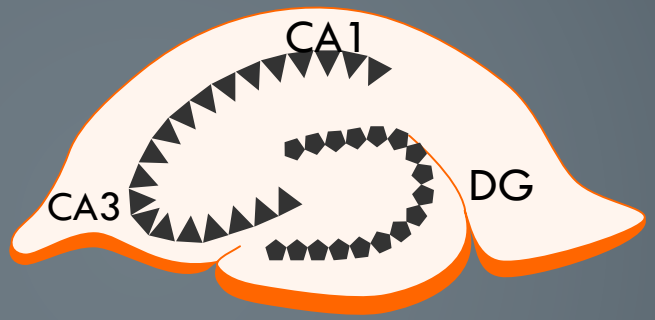
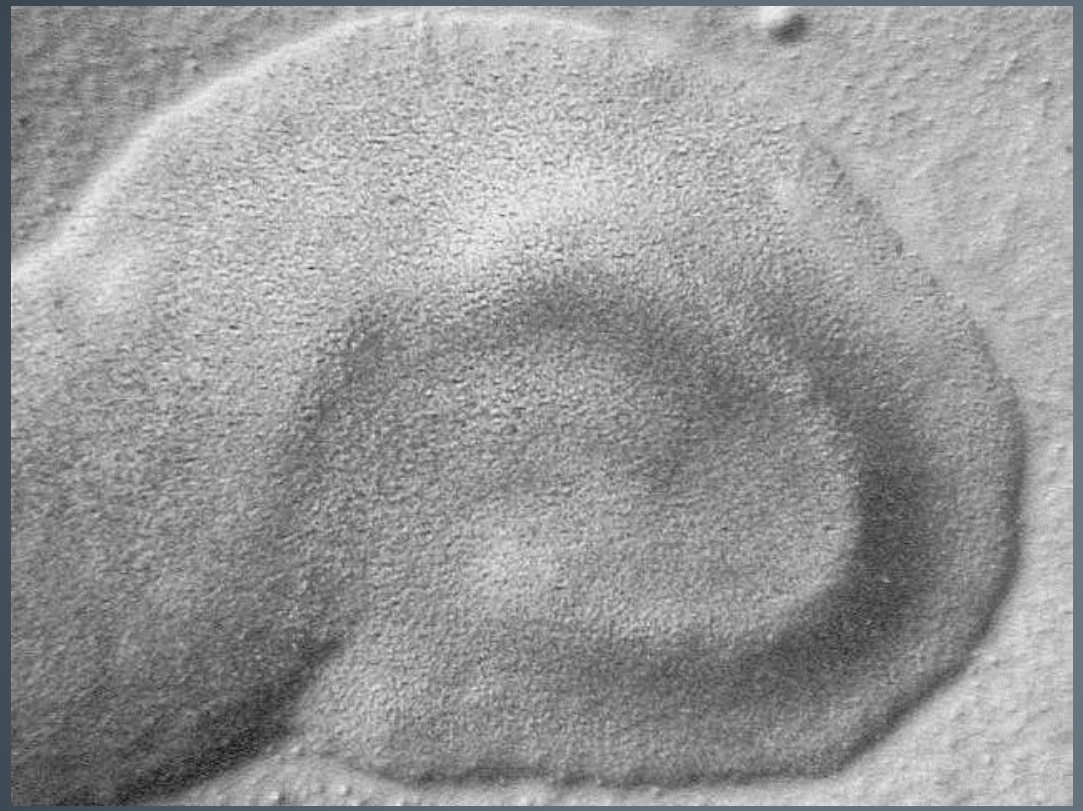


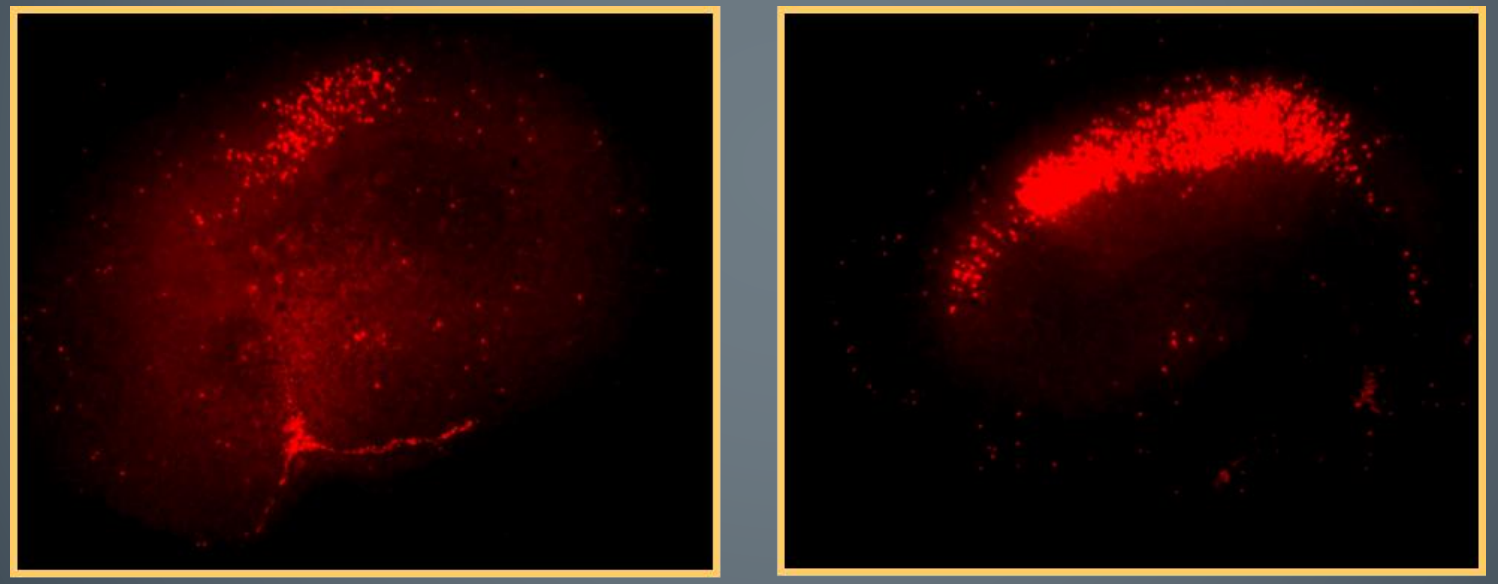
- Rodent model to study behavioral effects (and pharmacological interventions)

Organotypic Hippocampal Slice



- Taken from neonatal rat
- Retains many of normal cells and connections found in brain
- Importance of the hippocampus –
  - plays a key role in learning and memory.

ETOH WD causes hippocampal damage



Control

ETOH WD

Rodent models of FAS

- Show many similar characteristics in terms of CNS damage and behavioral deficits in human populations.

Courtesy: Ed Riley

2 approaches to pharmacotherapy

- Administer agent/drug during ETOH exposure or shortly after (during ETOH withdrawal)
  - reduce damaging effects- neuroprotection
- Administer pharmacotherapy to juvenile/adolescent/adult to improve outcome after prenatal exposure
  - ex. Can behavior/performance improve with pharmacotherapy?

Ongoing research

- Novel agents synthesized at Univ of Kentucky as part of a medication development project…
- Natural alkaloids from plants
- Drugs in clinical trials for other purposes

Mechanisms being examined

reducing NMDAr (glutamate) activity

glutamate is the major excitatory neurotransmitter in the CNS

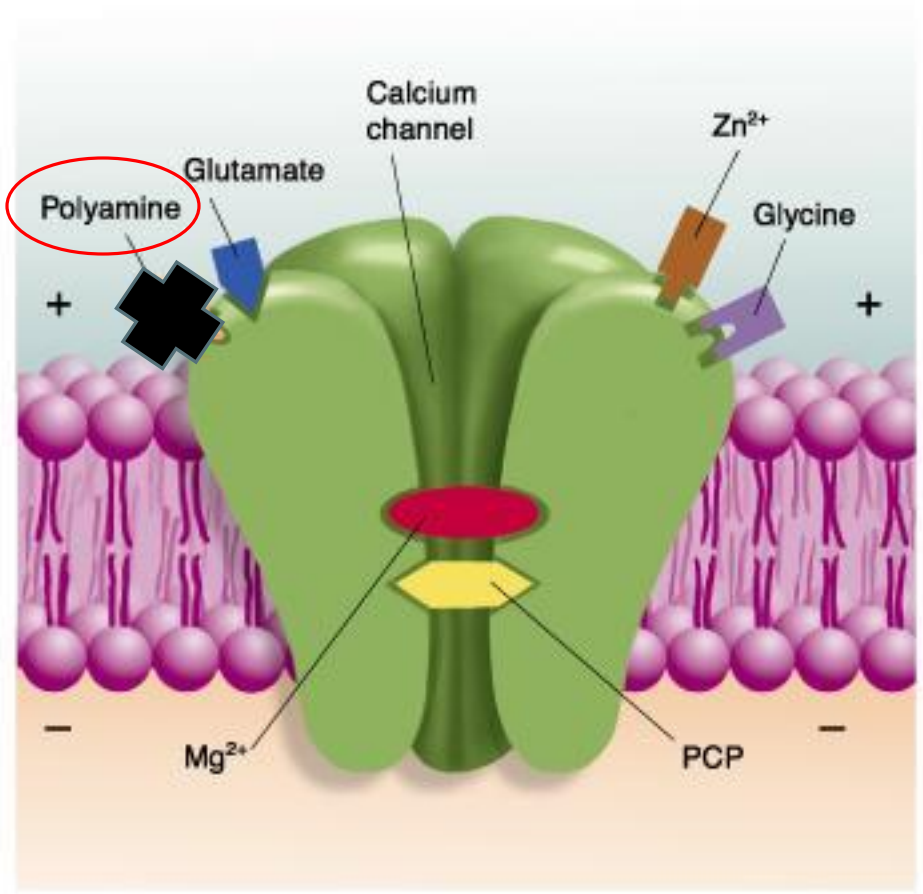
Chronic ETOH reduces glutamate activity

during ETOH withdrawal, there is compensatory response with too much activity – resulting in neuronal damage/death

▶ A Schematic Illustration of an NMDA Receptor, with Its Binding Sites

polyamines are released during EWD and contribute to the neurotoxicity during EWD

Reducing polyamines or blocking the polyamine site can reduce neuronal death/damage

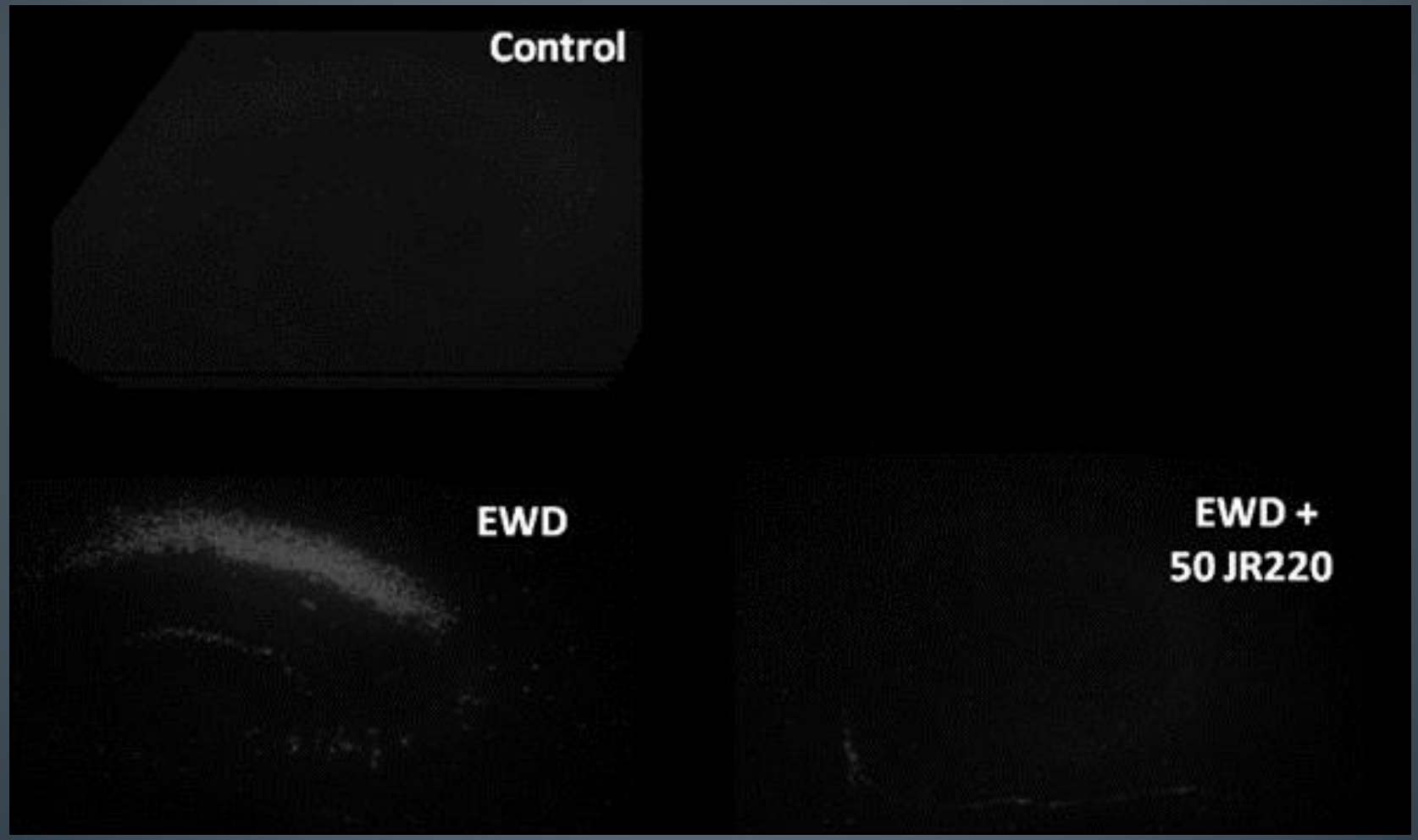


JR 220

- Synthesized at University of Kentucky as part of a library of 1000's of compounds based loosely on agmatine-like structure

- aryliminoguanidine

JR 220 blocked EWD neurotoxicity in hippocampal slices

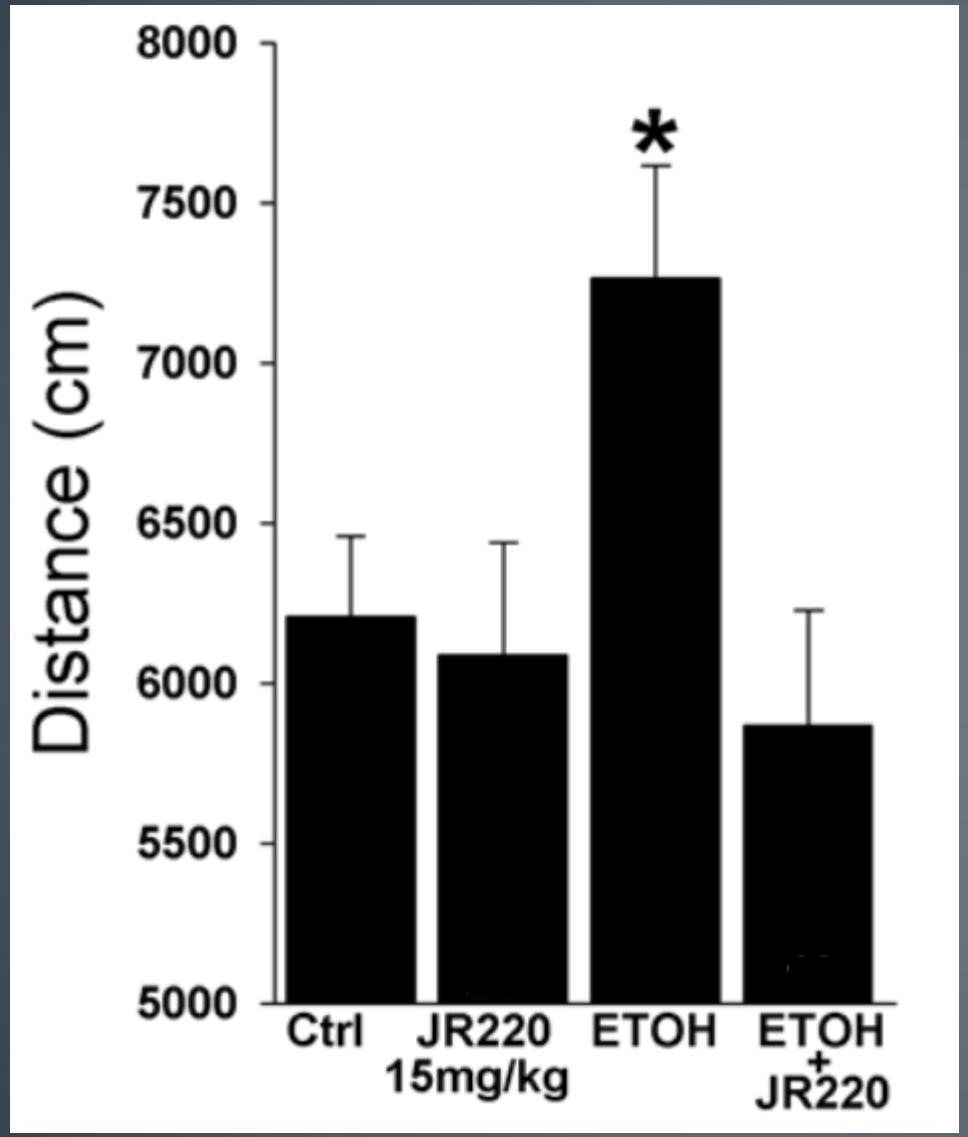


Our typical design

- ETOH exposed offspring
- ETOH+ JR220- typically given after ETOH treatment (so during ETOH WD)
- JR 220 alone -- to ensure JR 220 has no effects itself
- Non-treated Control

Behavioral results

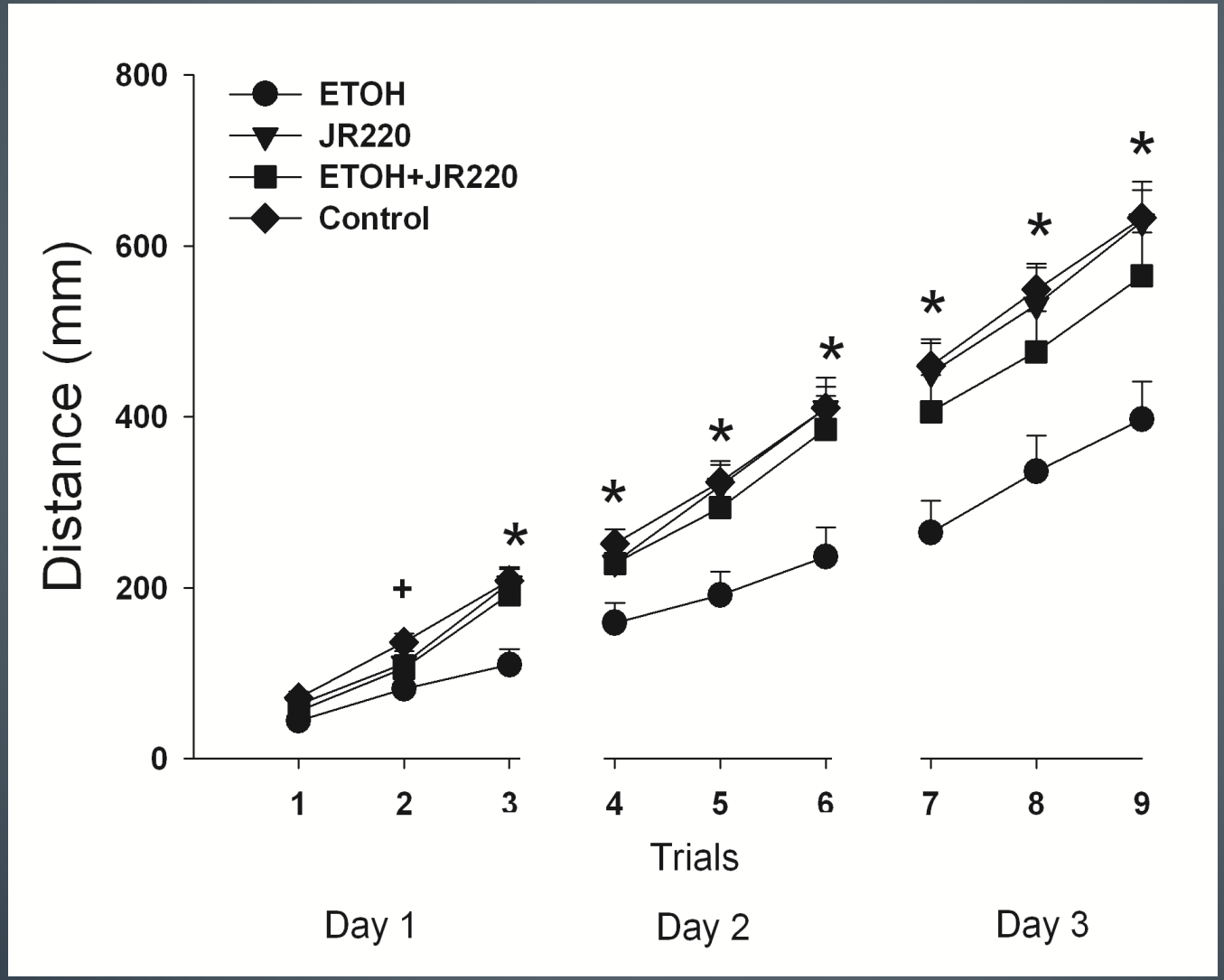
Open field used to assess activity/hyperactivity



JR 220 administered during early development eliminated the hyperactivity displayed by ETOH exposed offspring

Balance and gross motor coordination

JR 220 administered early in development improved balance and coordination in ETOH exposed offspring



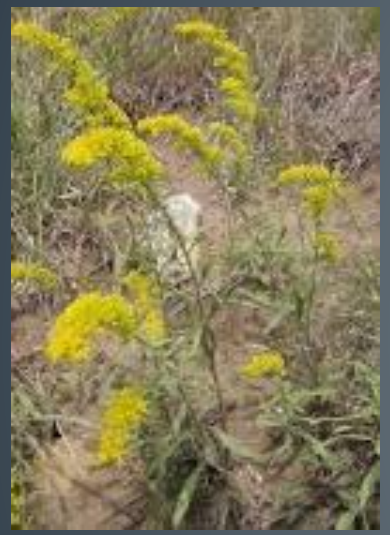
Current status of polyamine manipulations

- JR 220
- Other drugs that block or reduce polyamines

A 2nd mechanism being studied

activating certain types of acetylcholine receptors

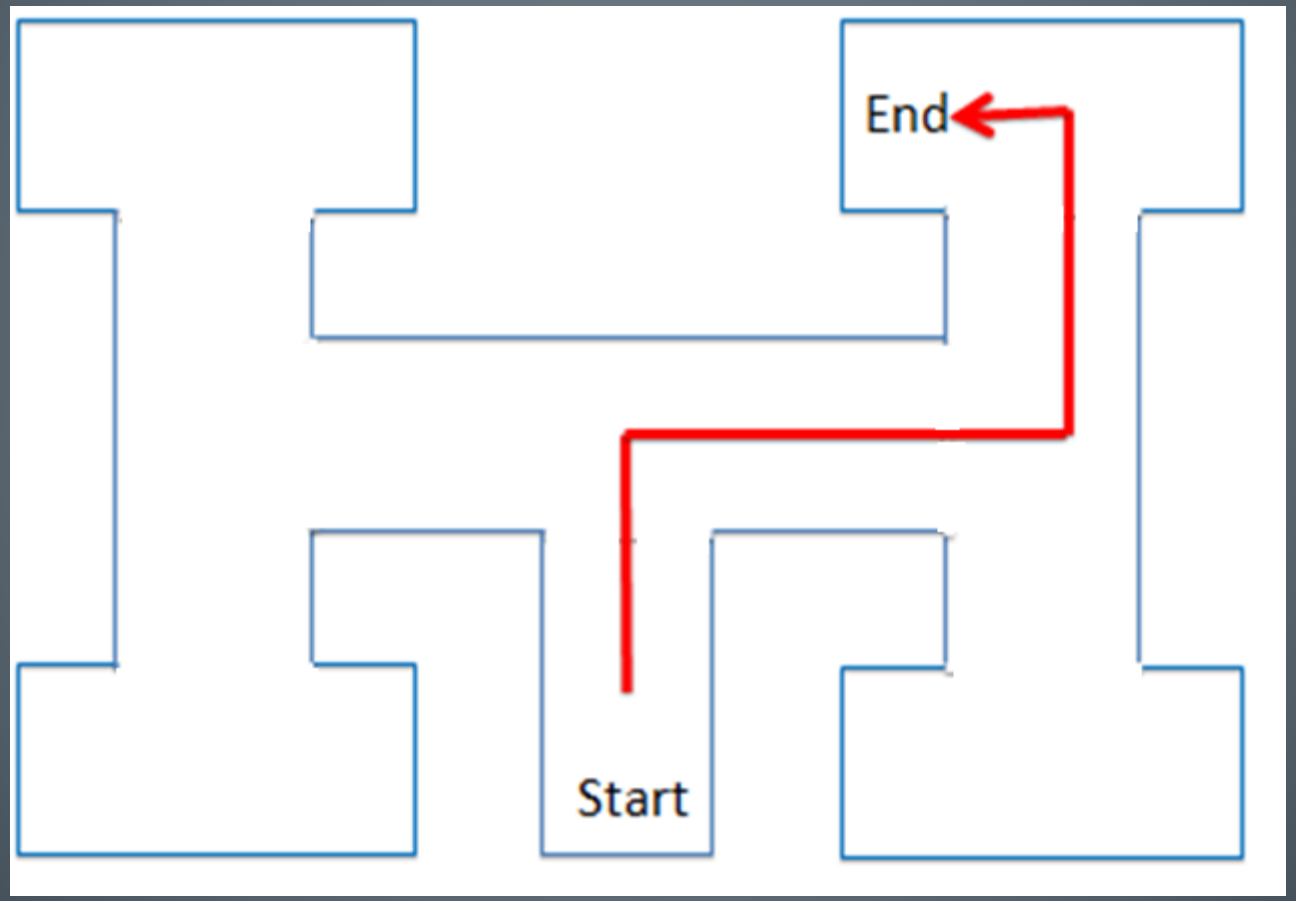
KY native plant library

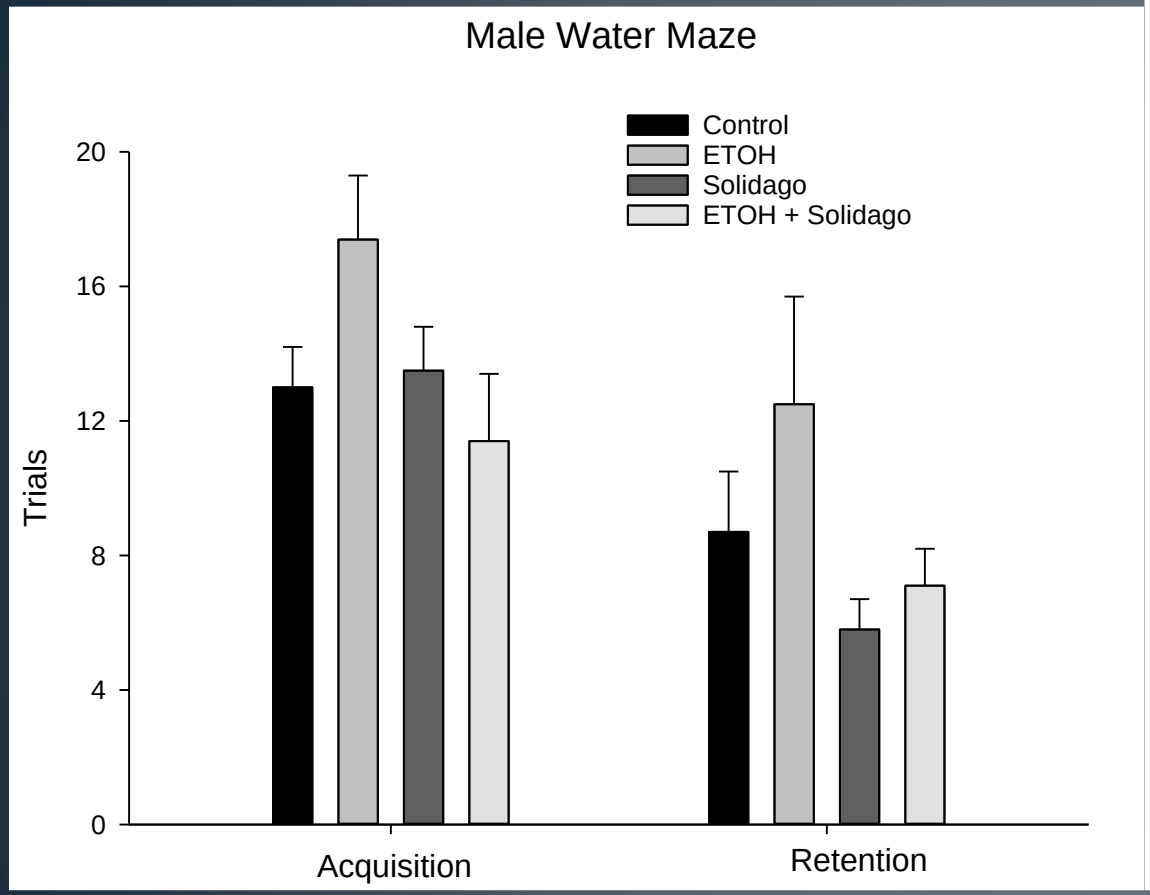


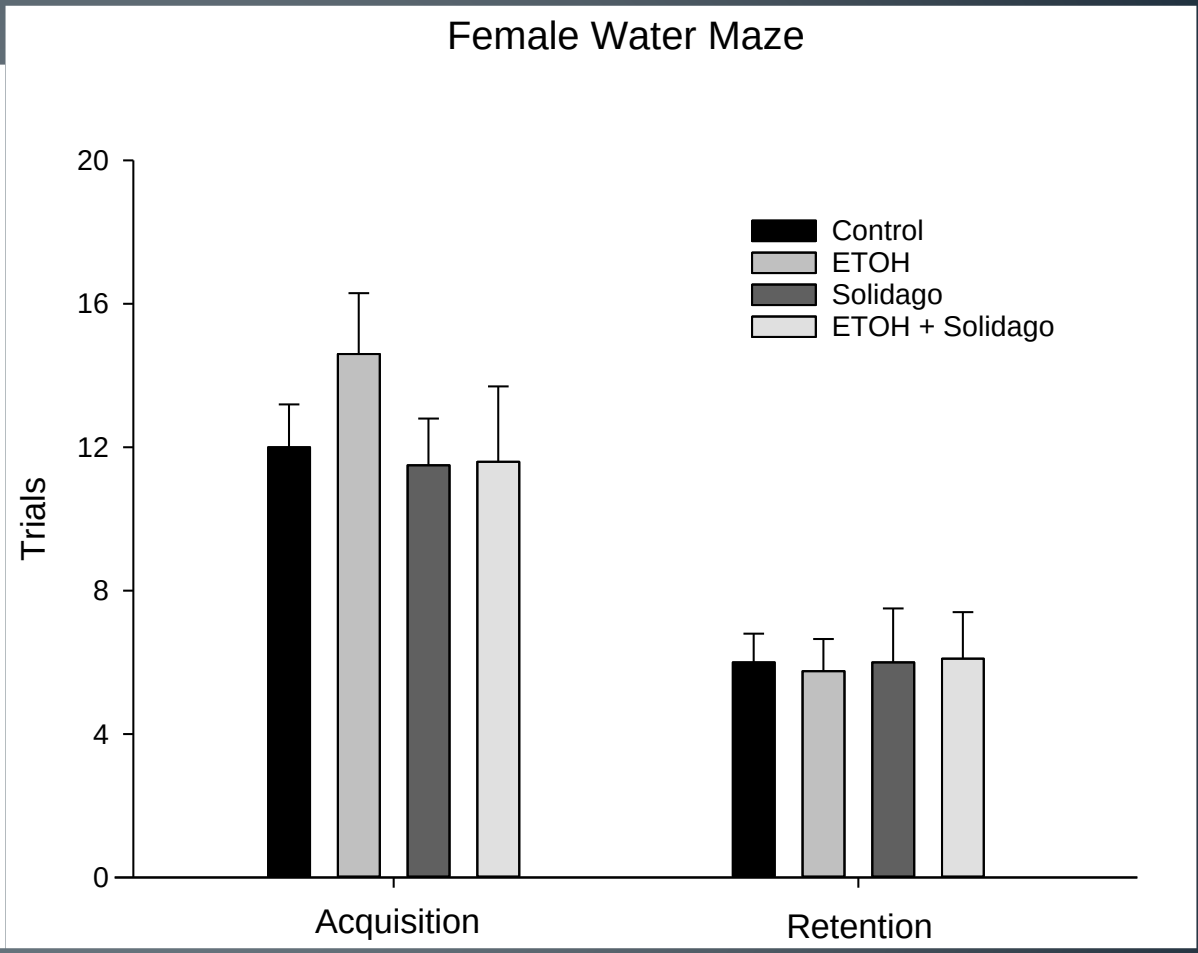
Solidago nemoralis – flavonoid extract of Gray goldenrod

alpha 7 nicotinic receptor agonist

A one day water maze test for spatial learning







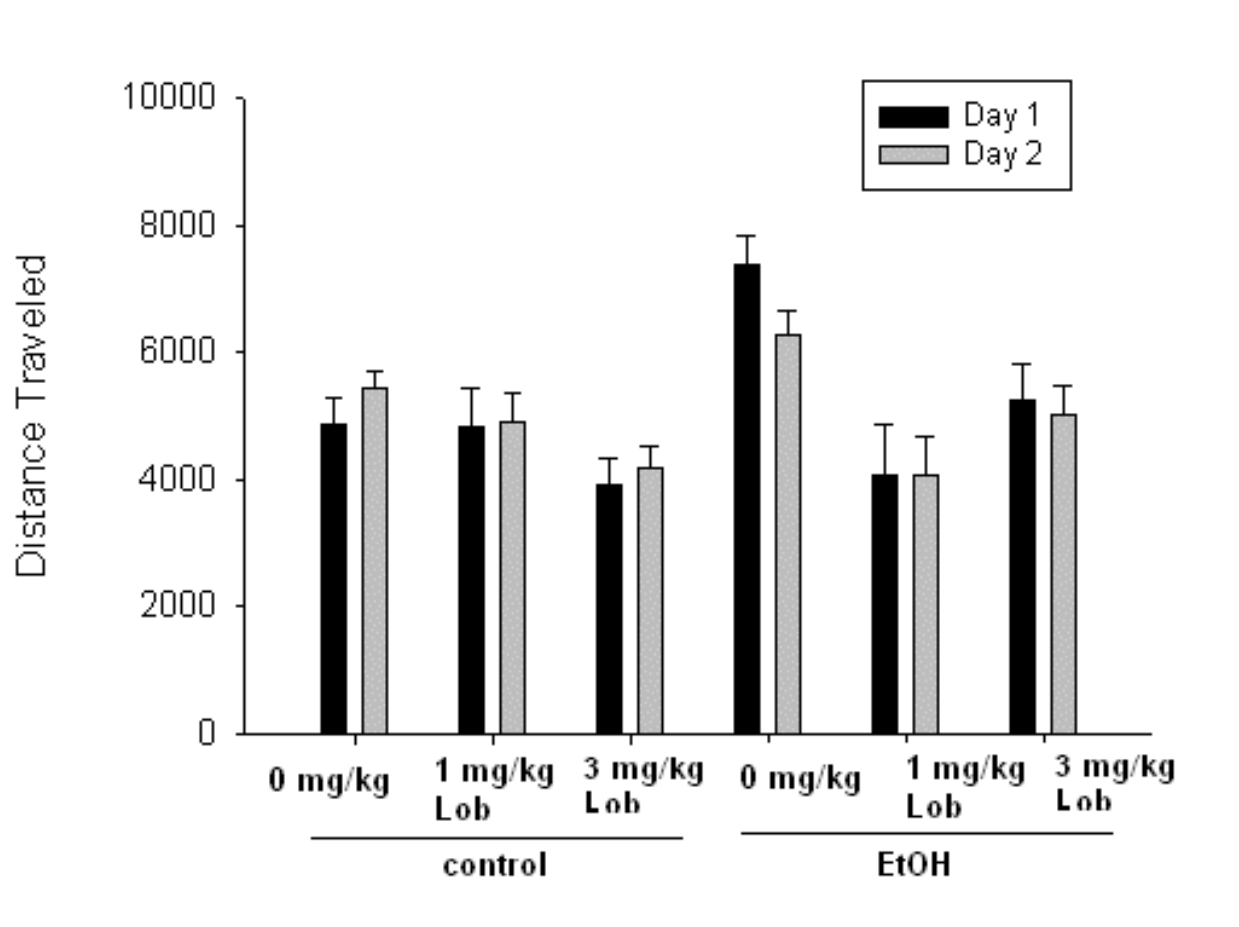
Solidago nemoralis extract improved spatial learning in ETOH exposed rats (and in males, 24 hr retention was also improved)

2 approaches to pharmacotherapy

- Administer agent/drug during ETOH exposure or shortly after (during ETOH withdrawal)
  - reduce damaging effects- neuroprotection
- Administer pharmacotherapy to juvenile/adolescent/adult to improve outcome after prenatal exposure
  - ex. Can improve performance with pharmacotherapy?

Lobeline – alkaloid found in *Lobelia inflata* – Indian Tobacco

Lobeline works on DA (among other neurotransmitter systems) but is not a stimulant



Lobeline administered 30 min prior to testing reduced hyperactivity in ETOH exposed offspring yet had no effect in control rats

Summary

- Making progress on understanding mechanisms (and hence potential pharmacotherapies) on the effects of ETOH on the developing brain
- ETOH has numerous effects on the brain and so multiple mechanisms and approaches will likely be critical in reducing some of the damaging effects
- Being able to differentiate ADHD populations from FASD may be critical for testing pharmacotherapies.

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Thanks for Listening
Questions, comments?
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