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Preclinical Studies of Glucocorticoid Receptor Antagonists in the Treatment of Alcohol Dependence

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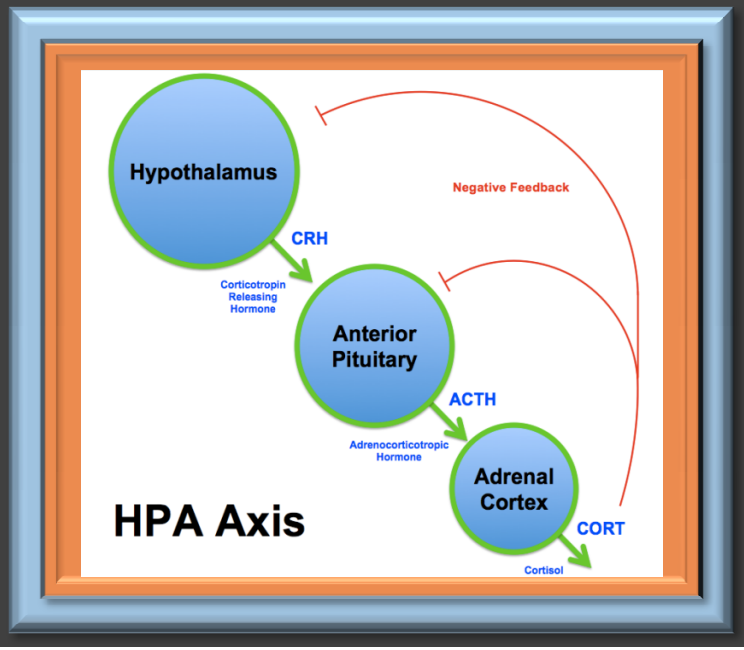
Current FDA Approved Treatments for Alcohol Dependence

- Antabuse
- Naltrexone
  - Vivitrol
- Acamprosate

- Alcohol Withdrawal
  - Benzodiazepines

Stress and Addiction

- HPA Axis and Addiction:
  - Cortisol / Corticosterone
  - Type 1: Mineralocorticoid receptors (MR)
    - High affinity
  - Type 2: Glucocorticoid receptors (GR)
    - Low affinity



Stress and Addiction

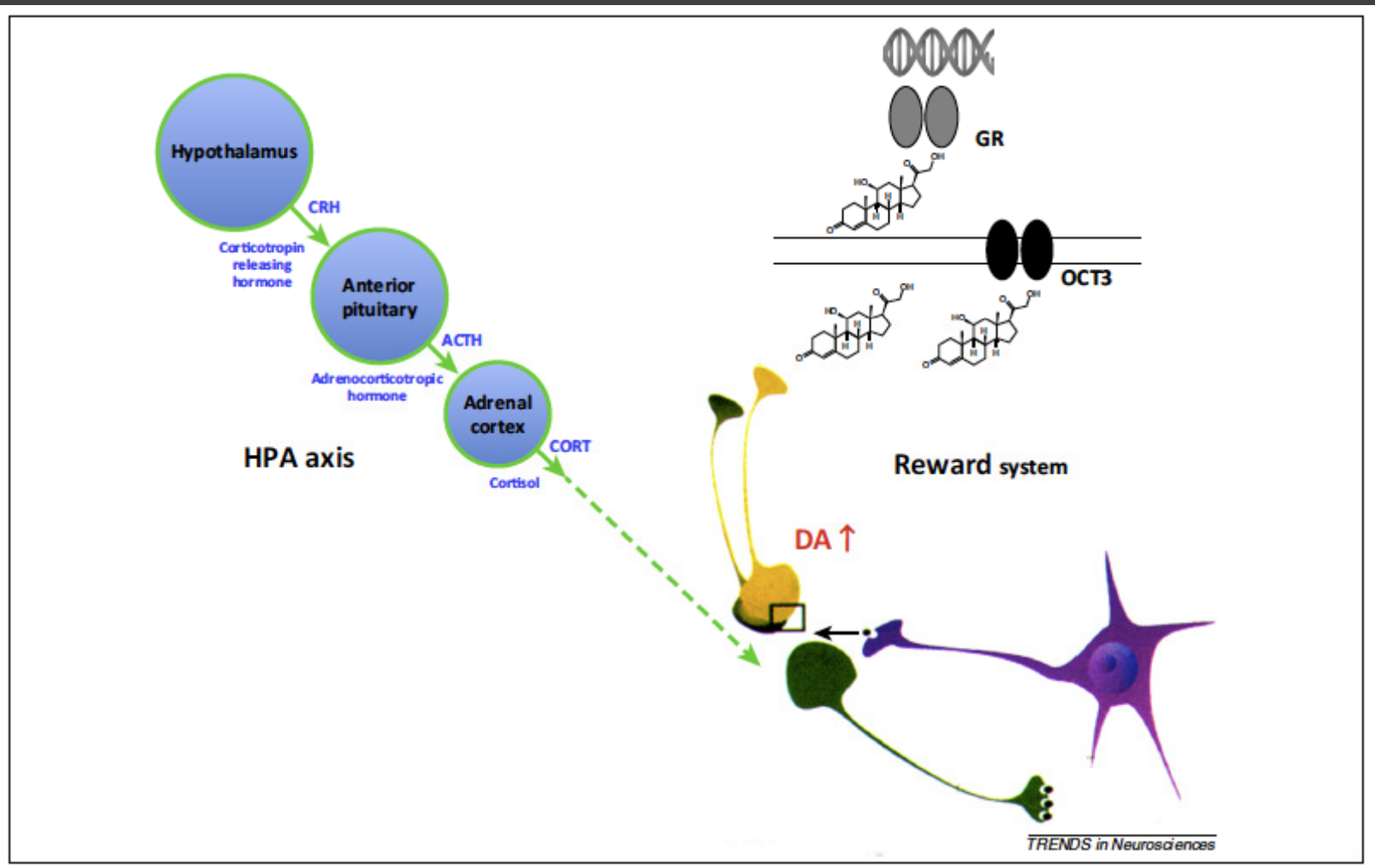
- Preclinical Studies:
  - Rats will self-administer CORT to physiological levels achieved with the presentation of stress.

    (Piazza et al, 1993)
  - Administration of CORT increases self-administration of psychostimulants

    (Goeders, 1996)
  - Administration of CORT or presentation of stressor increases self-administration of alcohol

    (Faulke et al, 1994)

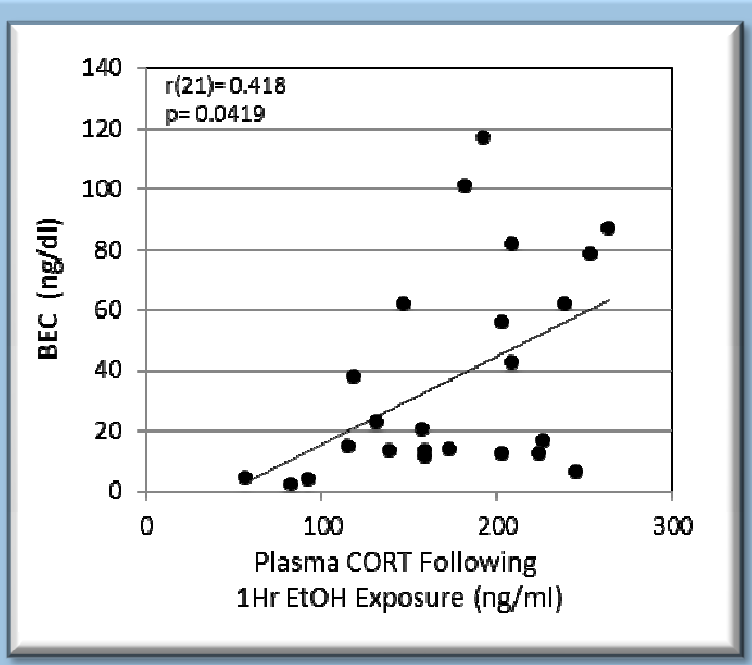
Potential Mechanism of CORT/DA Interaction



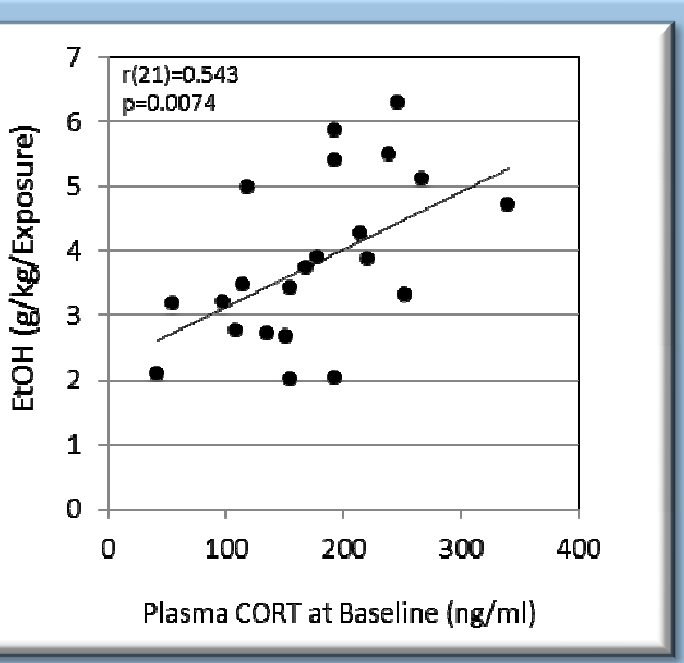
Spanagel, Noori, Heilig, 2014

Voluntary Intermittent Ethanol Consumption and CORT

BELs and plasma CORT levels following 1hr of EtOH exposure are positively correlated



Basal plasma CORT levels are associated with voluntary EtOH Consumption



Sharrett-Field et al., unpublished data

Slide 7

1

Recently found similar evidence that CORT response is + correlated with voluntary EtOH consumption.

CORT levels predict drinking durin 24 hr period
Animals that consumed high EtOh levels during first 24hrs of exposure demonstrated elevated levels of CORT

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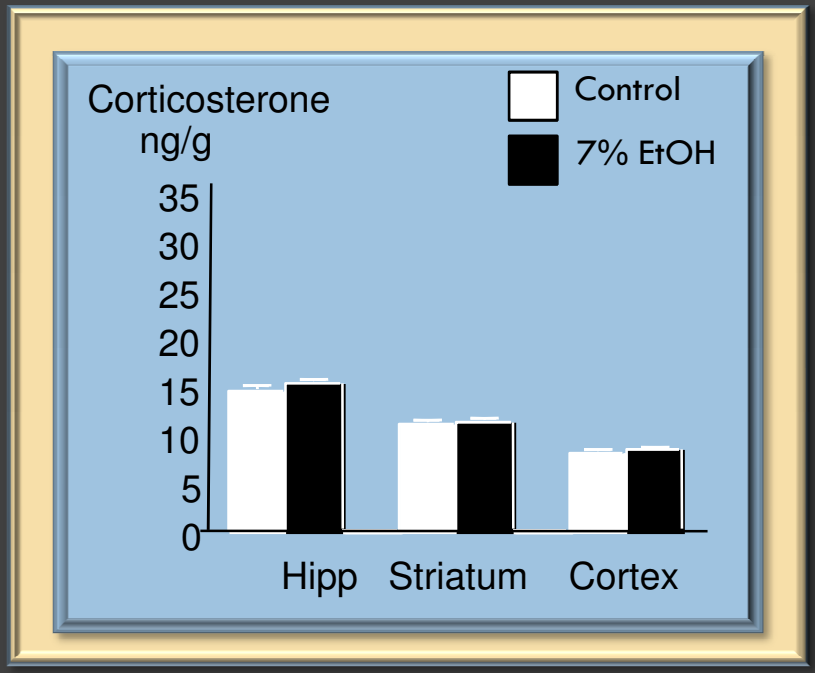
SL1

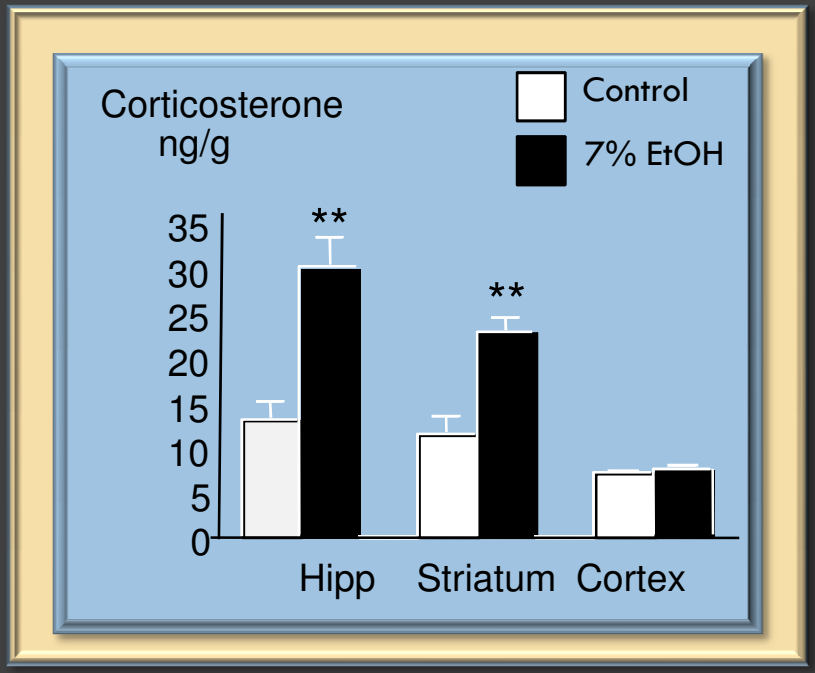
Forced Continuous Ethanol Consumption and Corticosterone

- Elevations in corticosterone differ across brain regions and are affected by abstinence.

3 week exposure ethanol via liquid diet



3 weeks ethanol via liquid diet
6 days of abstinence



(Little et al., 2008)

Slide 8

SL1

Importance of withdrawal in producing elevations CORT.

Different brain regions are exposed to different levels of CORT.

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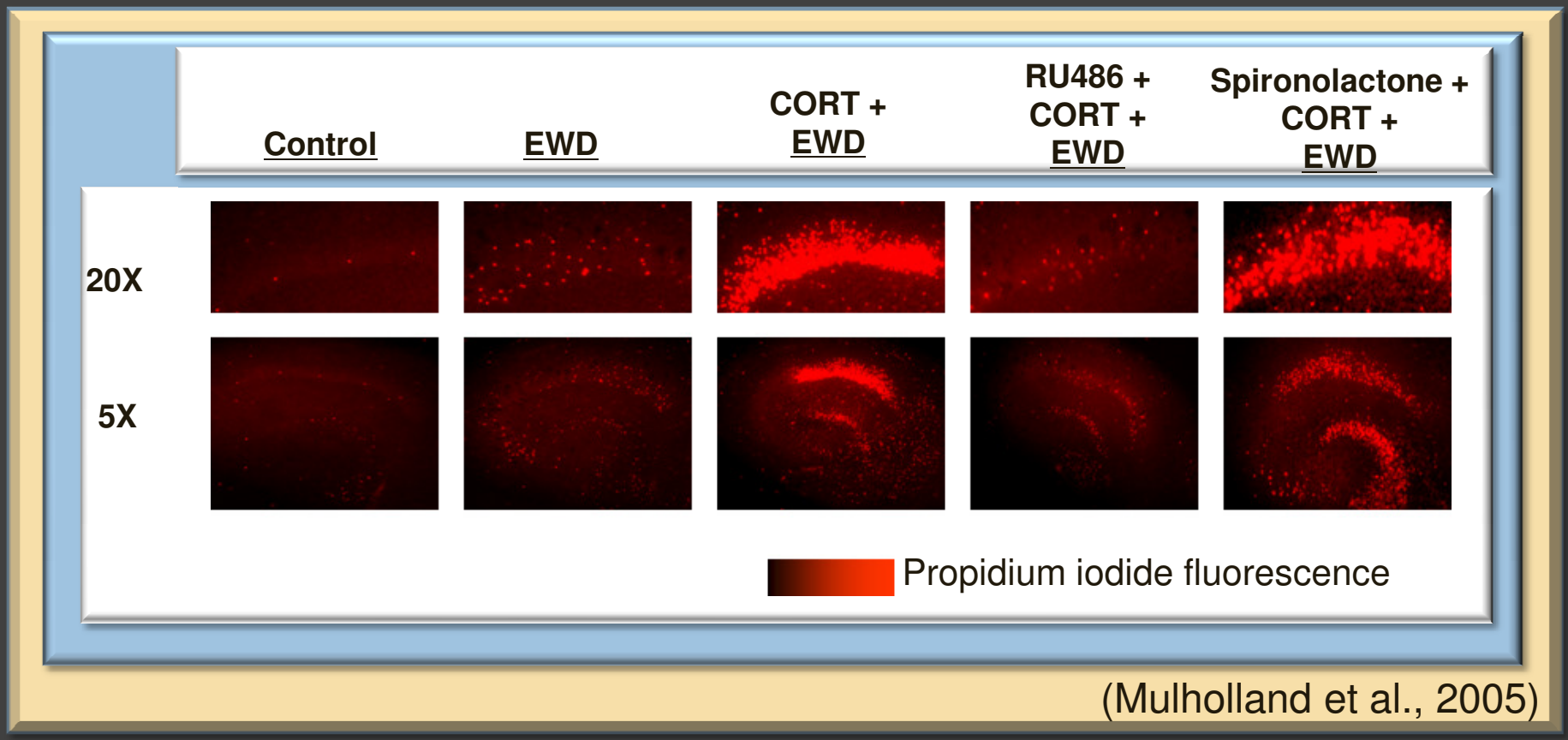
SL3

Ethanol withdrawal (EWD) induced neuronal damage reduced by RU486



(Mulholland et al., 2005)

- Organotypic hippocampal slice cultures
- CORT (1uM)exposure during EWD resulted in significant loss of cells, which is reduced by GR antagonism.

Slide 9

SL3 high levels of CORT are observed in the hippocampus

study looked at how these elevated levels of CORT are affecting the region during EWD

RU but not Spir reduced CORT+EWD effects, suggesting the effects are mediated by GR not MR

temporal lobe structures such as hippo are where many seizures begin during EWD. RU486 might be protective if given during EWD.

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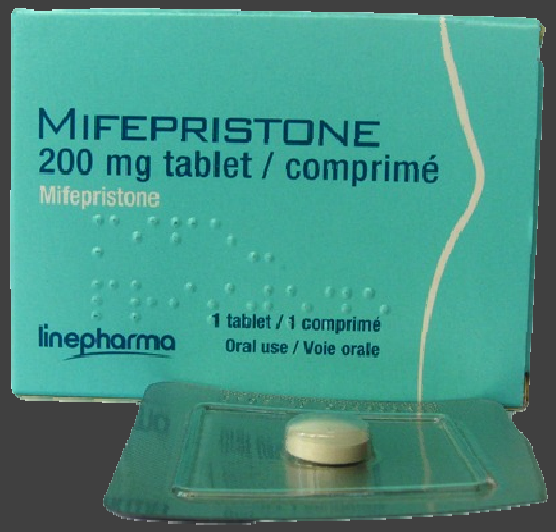
SL9

Glucocorticoid Antagonists

- GR receptor antagonist:
  - RU486 (Mifepristone)
    - Termination of pregnancy (Progesterone receptor)
    - Cushing's Syndrome
    - Depression with psychotic tendencies
    - Combat related PTSD
  - ORG34517 and ORG22189



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SL9 Points:

difference btwn high and low affinity indicates which will be implicated in mediating flux in CORT levels

receptors are intracellular, discuss where they are concentrated within the brain

difference in PR activity between RU486 and ORG analogs

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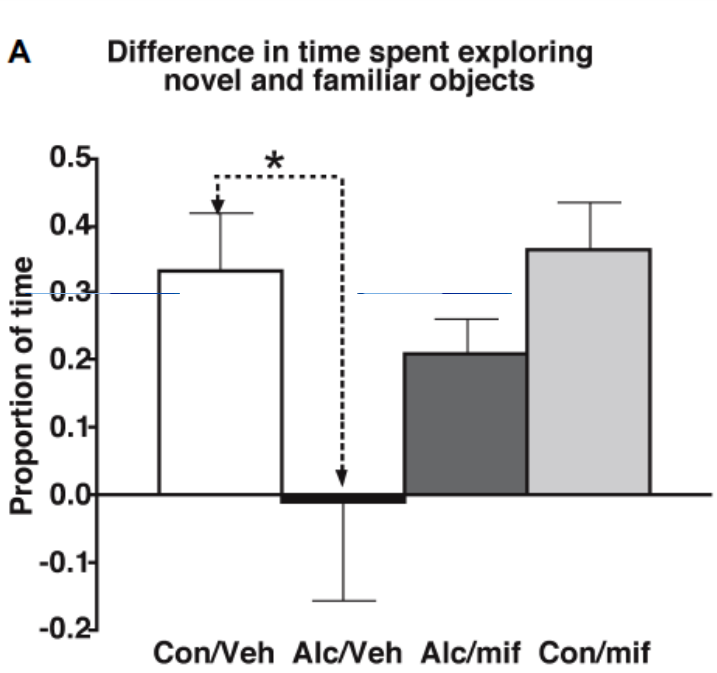
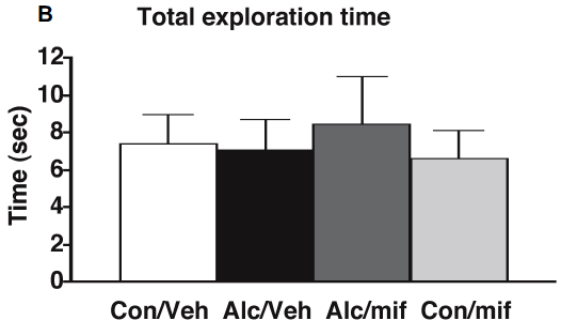
SL5

Cognitive effects of EWD and exposure reduced by RU486



Single administration of RU486 (mif) prior to EWD reversed alcohol induced alterations on the object recognition task.



Behavior assessed 8-10 days following withdrawal from 34 weeks of chronic alcohol treatment in CJ57 mice

(Jacquot et al., 2008)

Slide 11

SL5 These are CJ57 mice, 34 weeks of exposure.
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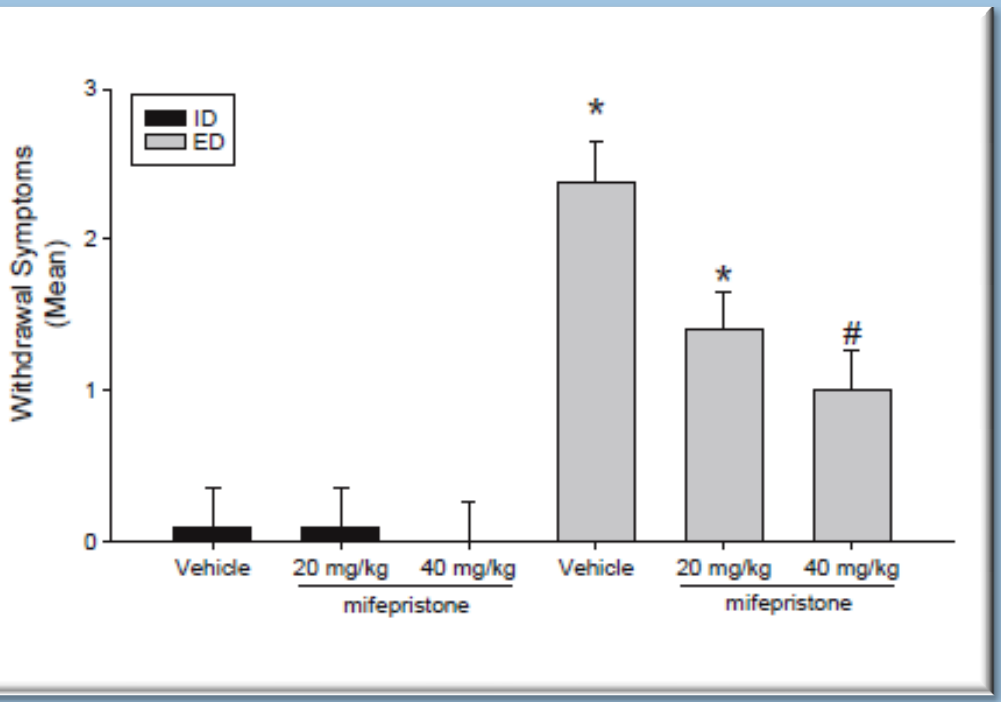
SL6

Behavioral effects of EWD reduced by RU486

4 day binge exposure:
Ethanol administered via gavage 3 times daily
Injections of RU486 or vehicle given once daily prior to first daily ethanol dose

- Tremor
- Splayed paws
- Rigidity
- "Wet dog shakes"



(Sharrett-Field et al., 2013)

Slide 12

SL6 RU456 can protect from cognitive effects if given prior to EWD, but can also reduce the behavioral effects associated with EWD. Important bc benzos currently most often prescribed drug given during detox, which does NOT protect against cognitive loss.
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SL8

Preference for alcohol is reduced by RU486

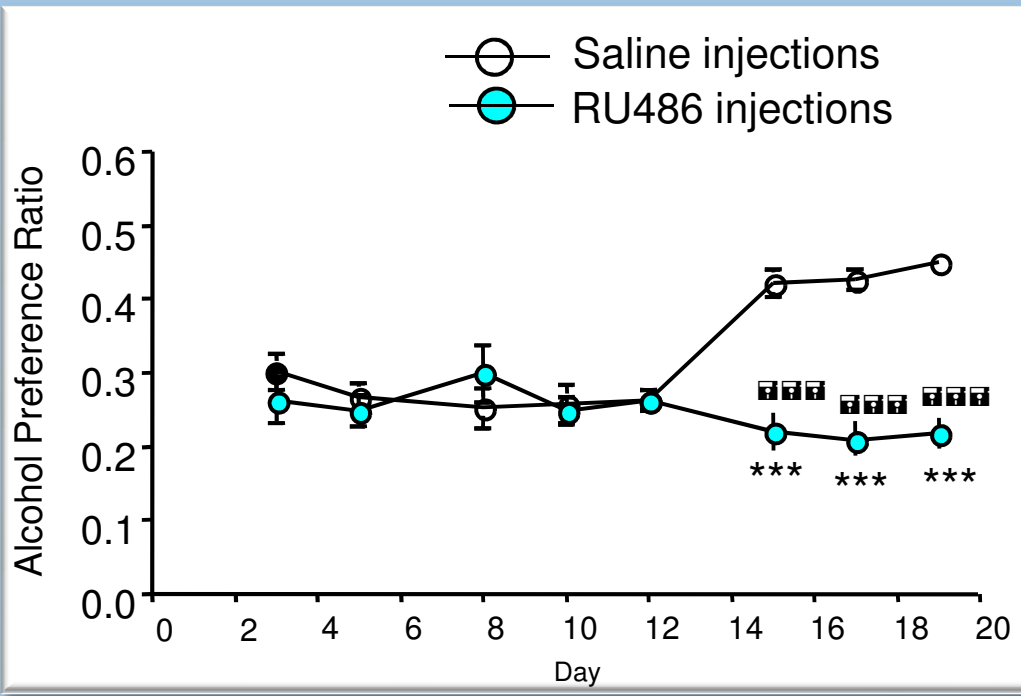
Low alcohol preferring mice

2 Bottle Choice:

8% EtOH or tap water

Once daily i.p. injection

Saline or RU486



(O'Callaghan et al, 2005)

Slide 13

SL8 RU456 can protect from cognitive effects if given prior to EWD, but can also reduce the behavioral effects associated with EWD. Important bc benzos currently most often prescribed drug given during detox, which does NOT protect against cognitive loss.
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Summary

- Basal levels of CORT are predictive of voluntary ethanol consumption
- Exposure to and withdrawal from chronic ethanol administration elevates levels of CORT
- Elevations of CORT during EWD produces cell loss in the hippocampus, *in vitro*.
- Administration of RU486 during EtOH or EWD:
  - Reduce cognitive deficits
  - Reduce behavioral signs of EWD
- RU486 reduces ethanol preference

Human Trials

- Co-Investigators- Hilary Little and Colin Drummond
- Participants
  - Alcoholics entering Alcohol Treatment Units for detoxification
    - DSM-IV for 5 or more years
    - Male aged 18-60 years
  - Randomized double blind trial
- Treatment
  - RU486 or placebo given upon drinking cessation and for following two weeks
- 12 month trial
  - Weeks 1-4:
    - Several assessments of withdrawal severity
    - Depressive symptomology
    - Sleep disturbances
    - Cognitive assessment
  - Follow-up at 3, 6, 12 months
    - Abstinence & relapse
    - Depressive symptomology

Acknowledgements

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  - NIAAA
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- Hilary Little
  - NIAAA
    - Grant: AA13932
  - Medical Research Council

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