Glucocorticoid Receptor Regulation of Binge-like Ethanol Intake

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Abstract

Glucocorticoid receptors (GR) have emerged as an important target for alcohol abuse. Dependence-induced escalations in alcohol intake can be prevented by administration of GR antagonists, but these same compounds have had little effect in non-dependent animals. Here, we investigated the role of GR in binge-like ethanol intake in the High Drinking in the Dark (HDID-1) line of mice and their founder line, HS/Npt.

Mice were administered compounds targeting the GR system in a modified 2-day Drinking in the Dark task. If ethanol intake was reduced, serial testing of water and saccharin intake were conducted. GR antagonism (mifepristone & CORT113176), but not FKBP51 inhibition (SAFit2), selectively reduced binge-like ethanol intake and blood ethanol concentrations (BECs) in the HDID-1 mice. GR antagonism did not reduce ethanol intake or BECs in the HS/Npt mice, suggesting that GR may have become sensitized through the selection process.

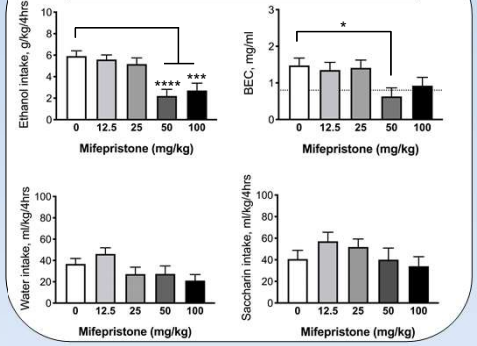
We further investigated whether GR antagonism was altering ethanol's aversive effects by testing HDID-1 mice in ethanol conditioned taste (CTA) and place aversion tasks (CPA). Although HDID-1 mice continued to show an attenuated aversive response to a moderate dose of ethanol (2 g/kg), as demonstrated previously, GR antagonism did not alter ethanol CTA or CPA.

Methods & Results

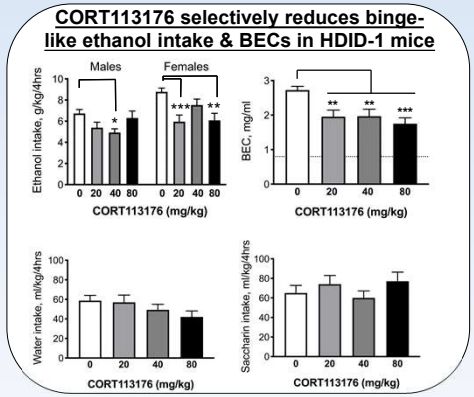
Drinking in the Dark (DID): HDID-1 or HS/Npt mice (M+F) were given a single bottle 3 hours after lights out containing either 20% ethanol, water, or 8.5 mM saccharin. Animals received food and water ad libitum outside limited access testing.

Week 1	2-Day DID: Ethanol	Drug on Day 2
Week 2	2-Day DID: Water	Drug on Day 2
Week 3	2-Day DID: Saccharin	Drug on Day 2

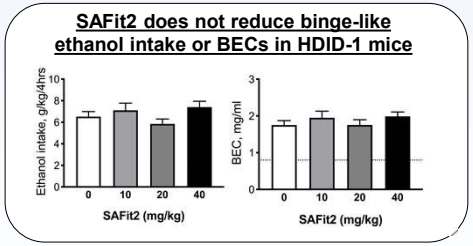
Mifepristone selectively reduces binge-like *ethanol intake* & BECs in HDID-1 mice



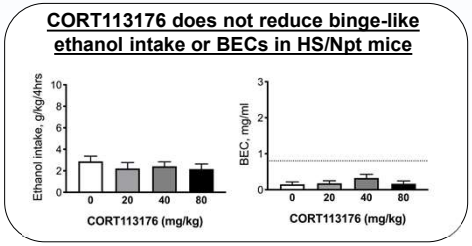
CORT113176 selectively reduces binge-like ethanol intake & BECs in HDID-1 mice



SAFit2 does not reduce binge-like ethanol intake or BECs in HDID-1 mice



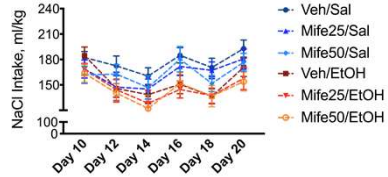
CORT113176 does not reduce binge-like ethanol intake or BECs in HS/Npt mice



Ethanol Conditioned Taste Aversion (CTA): HDID-1 mice (M+F) were tested for development of CTA to a novel NaCl drinking solution following paired injections with (a) saline or 2 g/kg EtOH, and (b) vehicle or mifepristone (25 or 50 mg/kg).

Habituation	7 days of 2-hr scheduled H2O access			
Pre-Conditioning	Day 8: 1-hr NaCl	Day 9: 2-hr H2O		
Conditioning	Day 10: 1-hr NaCl, injections	Day 11: 2-hr H2O	X 4 cycles	
Preference	Day 20: 1-hr NaCl			

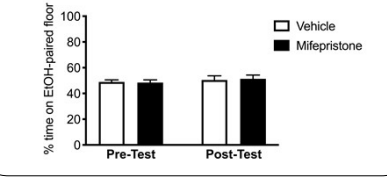
Mifepristone does not affect the acquisition of ethanol CTA in HDID-1 mice



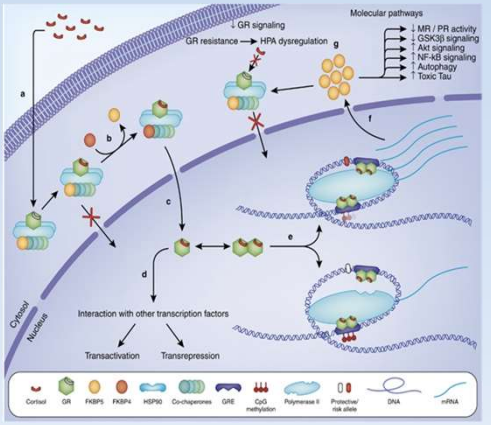
Ethanol Conditioned Place Aversion (CPA): HDID-1 mice (M+F) were tested in an ethanol CPA procedure, where 2 g/kg EtOH was paired with a contextual environment during conditioning and mifepristone (50 mg/kg) was administered on test day.

Habituation	30 min free access to both sides of chamber		
Conditioning (X 4 cycles)	Day 2: 5 min in EtOH-paired chamber	2 g/kg Ethanol	
	Day 3: 5 min in saline-paired chamber	Saline	
Preference	30 min free access to both sides of chamber	Vehicle or Mifepristone (50 mg/kg)	

Mifepristone does not affect the expression of ethanol CPA in HDID-1 mice



Pathway of Interest



Source: Zannas et al, *Neuropsychopharmacology* 2016

Conclusions

- Mifepristone and CORT113176 reduced non-dependent binge-like ethanol intake in HDID-1 mice
  - These are the first data to suggest GR antagonism could reduce non-dependent excessive alcohol intake, and suggest a role for GR activity in the genetic susceptibility to binge-like drinking
- CORT113176 did not reduce binge-like ethanol intake in the founder line, HS/Npt
  - These, and the above data, suggest that genetic changes elicited by selection for high BECs in HDID-1 mice have led to a sensitized response to GR antagonism
- Mifepristone did not enhance ethanol CTA or CPA
  - HDID-1 mice show an attenuated response to the aversive effects of ethanol, but GR antagonism may not alter the perception of ethanol's aversive effects
- Further studies in our lab are aimed at delineating the mechanism by which GR antagonism reduces binge-like ethanol consumption in HDID-1 mice

Funding

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