EFFECTS OF THE ENVIRONMENTAL TOXICANT, PARAQUAT, ON BINGE-LIKE ALCOHOL DRINKING AND ALCOHOL-INDUCED LOCOMOTOR SENSITIZATION IN HIGH AND LOW-ALCOHOL-PREFERRING MICE

S. Enkh-Amgalan[1], J. M. Brown[2], R. M. Foguth[2], T. B. Syeda[2], J. R. Cannon[2], J. A. Chester[1]
[1]Department of Psychological Sciences, [2]School of Health Sciences | Purdue University, West Lafayette, IN

Introduction

Aim: To explore motivation and reward-related disturbances in PD and excessive alcohol consumption using an environmental toxicant exposure model and mice susceptible for high alcohol preference.

Parkinson's Disease (PD):
- Characterized by significant dopaminergic (DA) neuron loss in the substantia nigra and motor impairments[1].
- Non-motor symptoms range from autonomic disturbances to neuropsychiatric comorbidities[1] (e.g. motivational dysregulations)[2].

Alcohol Use Disorder (AUD):
- Dysregulations in striatal dopaminergic systems underlie motivation and reward-related changes[3].
- Severe AUD is associated with movement disorders and transient parkinsonism[4].

Paraquat (PQ): A common herbicide toxic to DA and is an environmental risk factor for PD[5].
High (HAP) & Low (LAP) alcohol-preferring mice: A genetic animal model for inherited propensity toward risk for AUD[6]. Neurobiological processes related to excessive alcohol consumption may interact with PD-related changes.

Hypothesis: Paraquat exposed mice will show greater binge-like alcohol drinking[7] and alcohol-induced locomotor sensitization compared to non-exposed mice.

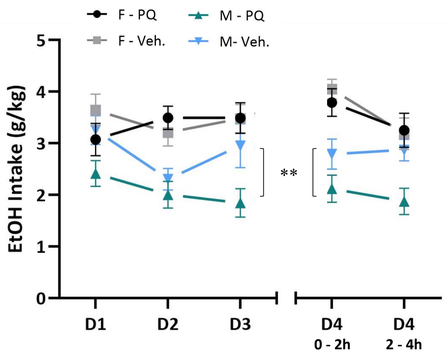
Methods

Exp. 1: "Drinking in the Dark" procedure that assesses binge-like alcohol drinking [8].
1. PQ/Vehicle (10 mg/kg) once a week for 3 weeks [9].
2. 7 days of acclimation to reverse light cycle [8]
3. 4 days of binge drinking for 2-4 hours a day [8].
4. Brain collection for neurochemical analysis after 1 day [10].

Exp. 2: Locomotor sensitization is a model for alcohol-induced neuroadaptation from repeated exposure [6].
1. PQ/Vehicle (10 mg/kg) once a week for 3 weeks [9].
2. 6 locomotor sensitization trials with EtOH/Saline (3 g/kg) [6].
3. Locomotor sensitization test with EtOH/Saline (2 g/kg) [6].

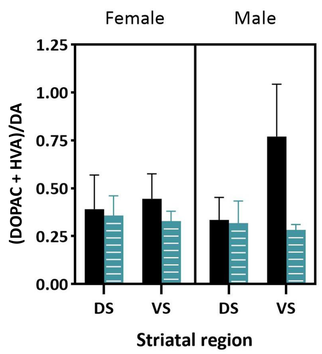
Exp. 1: Binge-like Alcohol Drinking In HAP Mice

Fig 1. 2-hour EtOH intake across 4 days



Means ± SEM
n = 17 - 24

Fig 2. DA and turnover in Dorsal (DS) and Ventral (VS) striatum



Means ± SEM
n = 6 - 10

Mixed ANOVA (Sex x PQ x Time)
- PQ x Sex, $p = 0.032$: PQ-exposed HAP males had significantly lower EtOH intake than non-PQ HAP males, $p = 0.002$. This effect was absent in females.
- In a subset of animals there was a trend of higher DA turnover in VS of PQ-exposed mice, and a lower 5-HT turnover in DS of PQ-exposed males (data not shown).

Discussion

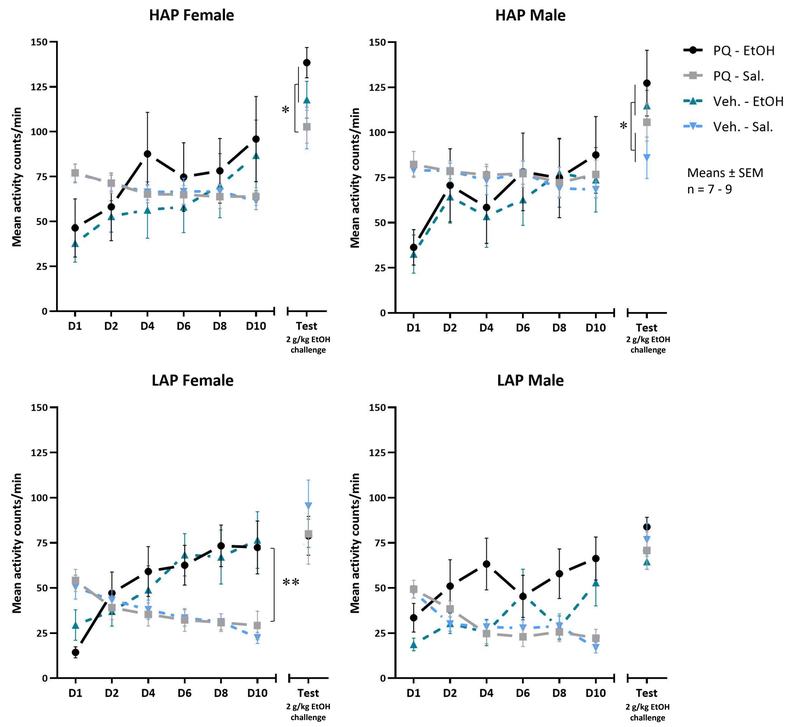
- PQ reduced binge-like alcohol drinking in male mice genetically susceptible for high alcohol preference, but not females.
  Motivation vs. Hedonic changes?
- Higher DA turnover in VS suggest a possible compensatory DA activity in response to PQ-induced damage.
- PQ-treated mice had greater variability in their alcohol-induced locomotor activity. Increase PQ exposure?

Acknowledgements

Funded by Center for Research on Brain, Behavior, and NeuroRehabilitation (CEREBBRAL)
Chester Lab at Department of Psychological Sciences
Cannon Lab at Department of Health Sciences

Exp. 2: Locomotor Sensitization in HAP and LAP Mice

Fig 3. Daily locomotor activity during induction (D1 - 10) and expression (Test) of locomotor sensitization



Mixed ANOVA (Line x Sex x PQ x EtOH x Time)
- No effect of PQ on activity and sensitization, $p > .05$
- Line x EtOH, $p = 0.008$: HAP mice with repeated EtOH showed sensitized stimulated response to 2 g/kg EtOH, $p = 0.002$. Repeated EtOH did not produce differences in LAP mice (collapsed across sex).
- Both lines developed tolerance, but LAPs developed sensitization to the initially sedating dose of 3 g/kg EtOH, $p < 0.001$ (collapsed across sex).

References

1.Deeb W, et al. (2019). Parkinson's disease: Diagnosis and appreciation of comorbidities. *Handb. Clin. Neurol*, *167*, 257–277.
2.Sinha N, et al. (2013). Impulsivity and apathy in Parkinson's disease. *J. Neuropsychol.*, *7*(2), 255–283.
3.Wise RA. (2009). Roles for nigrostriatal-not just mesocorticolimbic-dopamine in reward and addiction. *Trends Neurosci*, *32*(10), 517–524.
4.Cahill CM, et al. (2020). Alpha-Synuclein in Alcohol Use Disorder, Connections with Parkinson's Disease and Potential Therapeutic Role of 5' Untranslated Region-Directed Small Molecules. *Biomolecules*, *10*(10), 1465.
5.Cannon JR, et al. (2011). The role of environmental exposures in neurodegeneration and neurodegenerative diseases. *Toxicol. Sci*, *124*(2), 225–250.
6.Chester JA, et al. (2001). Effects of acamprosate on sensitization to the locomotor-stimulant effects of alcohol in mice selectively bred for high and low alcohol preference. *Behav. Pharmacol*, *12*(6-7), 535–543.
7.Yoshimoto K, et al. (2012). Administration of rotenone enhanced voluntary alcohol drinking behavior in C57BL/6J mice. Leg. Med, 14(5), 229–238.
8.Rhodes JS, et al. (2005). Evaluation of a simple model of ethanol drinking to intoxication in C57BL/6J mice. *Physiol. Behav, 84*(1), 53–63
9.Nixon AM, et al. (2018). HFE Genotype Restricts the Response to Paraquat in a Mouse Model of Neurotoxicity. *J. Neurochem*, *145*(4), 299–311.
10.Weera MM, et al. (2019). Genetic correlations between nicotine reinforcement-related behaviors and propensity toward high or low alcohol preference in two replicate mouse lines. *Genes Brain Behav.*, *18*(3), e12515