Impact of moderate alcohol consumption on paired helical filament-tau propagation in C57BL/6J mice

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Background

- Alzheimer's disease (AD) is the most common form of dementia and the seventh leading cause of death worldwide
- AD pathology is characterized by the aggregation of hyperphosphorylated tau protein into paired helical filaments (PHFs) and further into neurofibrillary tangles (NFTs)
- Previous research links moderate alcohol consumption to upregulation of human tau (p301L-tau) in transgenic mice

Objective: to better understand the impact of alcohol consumption on sporadic AD pathology

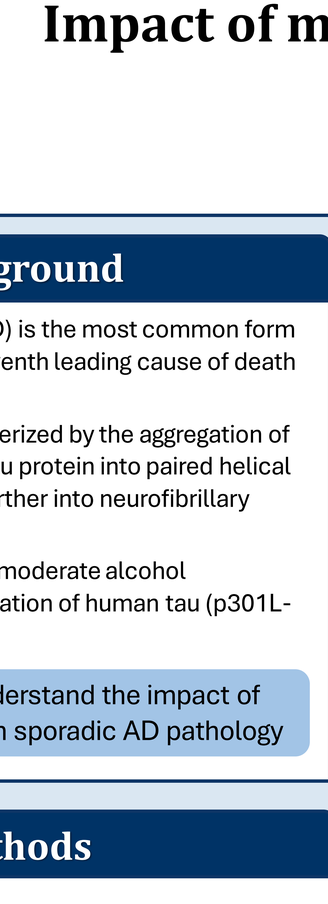
Methods

Female 16-week-old C57BL/6J mice received adeno-associated virus (AAV) containing GFP-2a-p301Ltau mRNA sequence in entorhinal cortex (EC)

Mice underwent four weeks of two-bottle choice home-cage drinking with access to only water or water and ethanol solution (20% v/v)

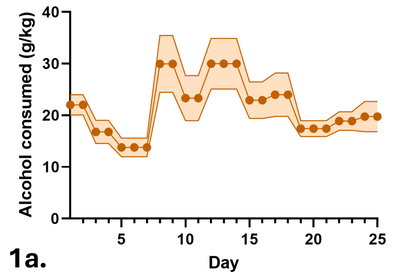
Sagittal brain slices were labeled via IHC with MC1 antibody (1°) [1:1000] followed by Alexa Fluor-647 goat anti-mouse antibody (2°) [1:1000]

GFP- and MC1-labeled cells were counted in central EC (CEnt), medial EC (MEnt), and hippocampus (CA1)



Results

Home-cage drinking



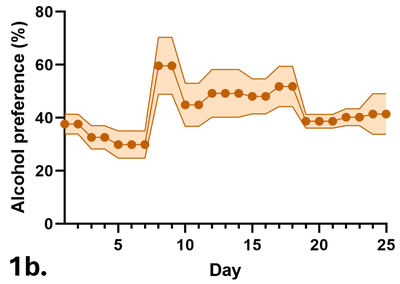


Figure 1a. Average daily alcohol intake ranged from 13.77 g/kg to 29.99 g/kg with a mean of 21.54 ± 1.06 g/kg/day.

Figure 1a-b. Significant effect of day on alcohol consumption [F (24, 150) = 2.422, $p < 0.05$] (**1a**) and preference [F (24, 150) = 1.628, $p < 0.05$] (**1b**).

PHF-tau expression

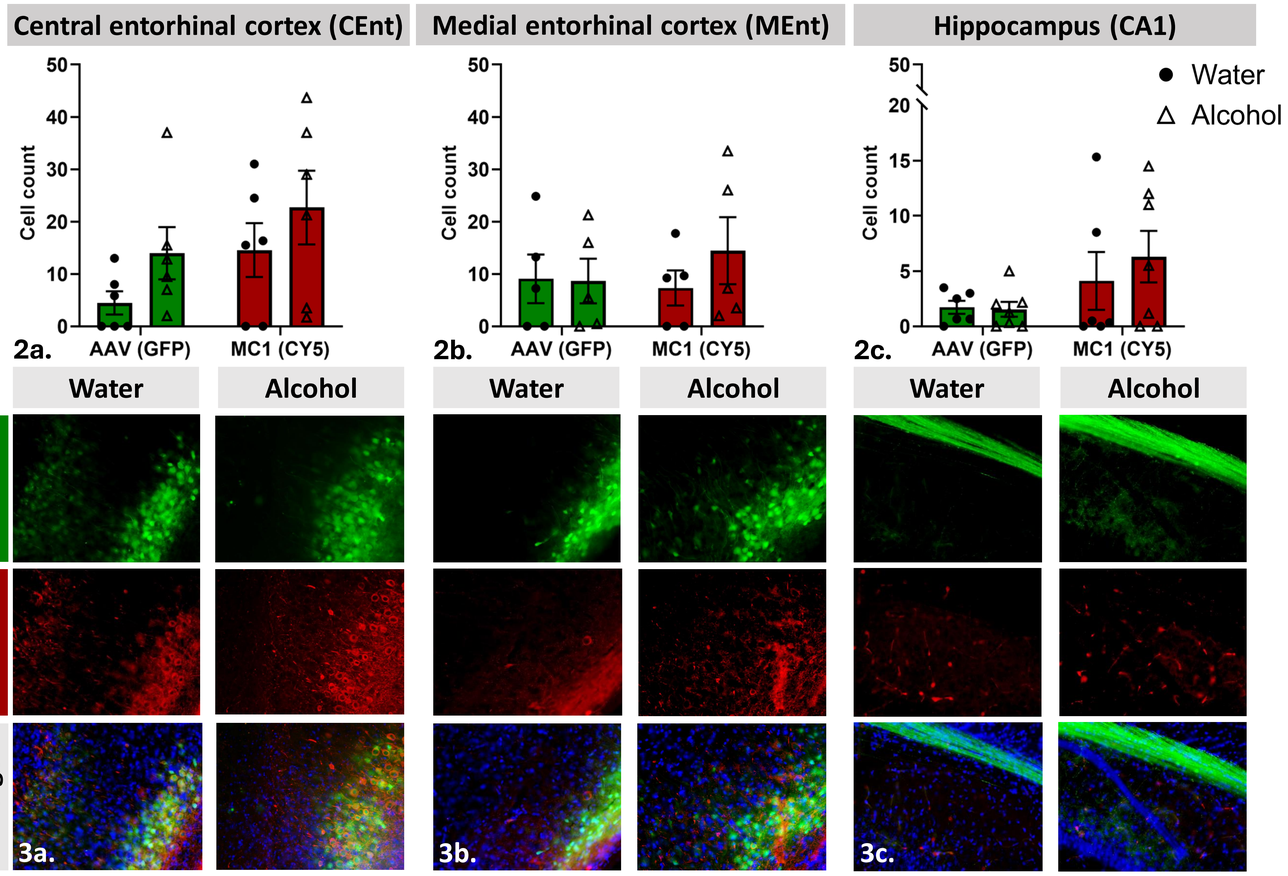


Figure 2a-c. Number of AAV+ and MC1+ cells in the CEnt **(2a)**, MEnt **(2b)**, and CA1 **(2c)** of water mice and alcohol mice; error bars represent standard error of mean (SEM).

Figure 3a-c. Sample images from the CEnt **(3a)**, MEnt **(3b)**, and CA1 **(3c)** of water mice and alcohol mice at 20X magnification. AAV+ cells shown in row 1; MC1+ cells shown in row 2; AAV+ cells, MC1+ cells, and DAPI-stained nuclei shown in row 3.

Summary and Conclusions

- No significant effect of fluid on number of AAV+ or MC1+ cells detected in CEnt, MEnt, or CA1
- Trends of increased expression in mice consuming ethanol and for the number of MC1+ cells in CEnt, MEnt, and CA1
- Significant effect of brain region on number of AAV+ cells [F (2, 18) = 5.587, $p < 0.05$] and MC1+ cells [F (2, 18) =6.573, $p < 0.05$]
- Alcohol consumption was congruent with C57BL/6J mouse strain and continuous access protocol

These findings suggest that **moderate alcohol consumption may potentially increase PHF-tau expression in C57BL/6J mice**; however, further studies with a larger sample size must be conducted to conclude a significant effect.

Future Directions

- Increase number of subjects to improve analytical power
- Analyze fraction of co-labeled cells
- Employ chronic intermittent ethanol exposure as a heavy drinking model

Acknowledgements

This work is supported by NIH NIAAA grants R01 AA028782 and R01 AA028782-03S1.