Antagonism of the Mineralocorticoid Receptor as a Potential Pharmacotherapy for Alcohol Use Disorder: Convergent Evidence from Rodent and Human Studies

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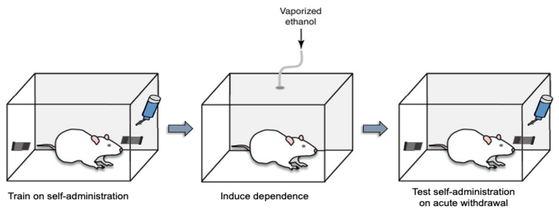
BACKGROUND

- Recent evidence suggests that the mineralocorticoid receptor (MR) and its endogenous ligand, aldosterone, may play a role in alcohol seeking and consummatory behaviors.
- MR antagonism may represent a new pharmacotherapy for alcohol use disorder (AUD). Spironolactone is an FDA approved and widely use MR antagonist.
- Aim: to investigate the effects of MR antagonism via spironolactone on alcohol use in rodents and humans.

METHODS

❑ Rodents

- **Study 1**: Operant alcohol self-administration (0.1 mL, 10% w/v ethanol) in male Wistar rats made dependent on alcohol (n=5) by chronic alcohol vapor exposure, as well as non-dependent rats (n=6) exposed to air only.
- Intraperitoneal injection of spironolactone (10, 25, and 50 mg/kg) before the test session.
- Replication with spironolactone (50 mg/kg) in a separate cohort of alcohol-dependent (n=7) and non-dependent (n=9) rats.



- **Study 2**: Drinking-in-the-dark paradigm (20% alcohol + 0.1% saccharin + 3% glucose) in male and female C57BL6J mice.
- Subcutaneous injection of spironolactone (25, 50, 100, and 200 mg/kg) before the test session.

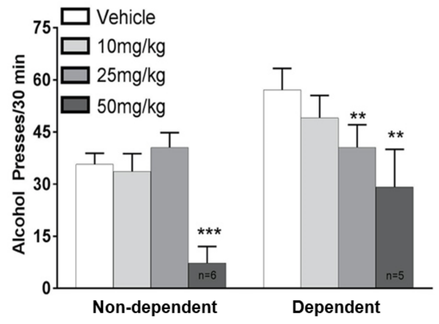
❑ Humans

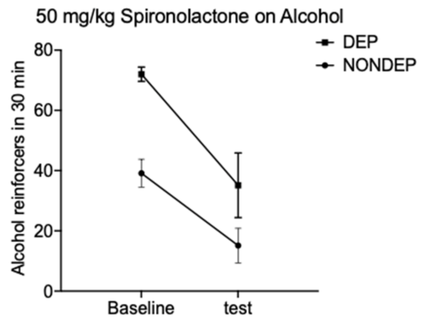
- **Study 3**: Kaiser Permanente Northern California
- Spironolactone-treated individuals (n=523) propensity score matched to up to 5 untreated individuals (n=2,305).
- Comparison of treated vs. untreated groups in Δ number of drinks per week from baseline to follow-up (DID: difference-in-difference).
- **Study 4**: US Veteran Birth Cohort
- Spironolactone-treated individuals (n=9,790) propensity score matched to up to 5 untreated individuals (n=31,579).
- Comparison of treated vs. untreated groups in Δ Alcohol Use Disorder Identification Test - Consumption (AUDIT-C) score from baseline to follow-up (DID).

RESULTS

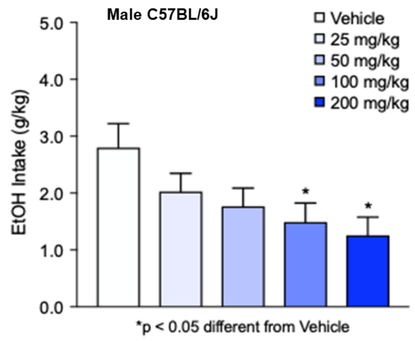
❑ Rodents

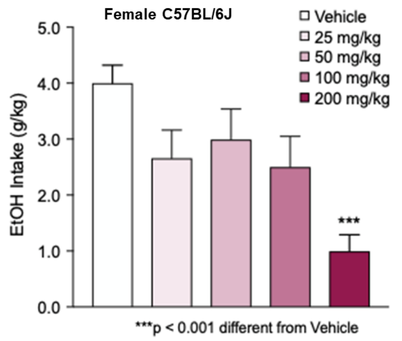
- **Study 1**: Spironolactone reduced alcohol self-administration in both alcohol-dependent and non-dependent male rats.





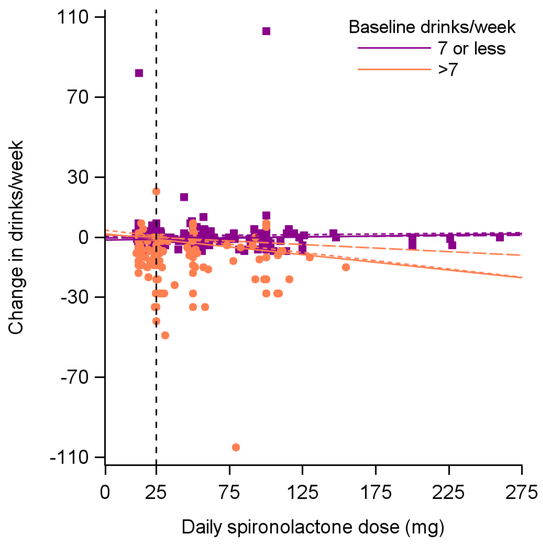
- **Study 2**: Spironolactone dose-dependently reduced alcohol binge drinking in both male and female mice.



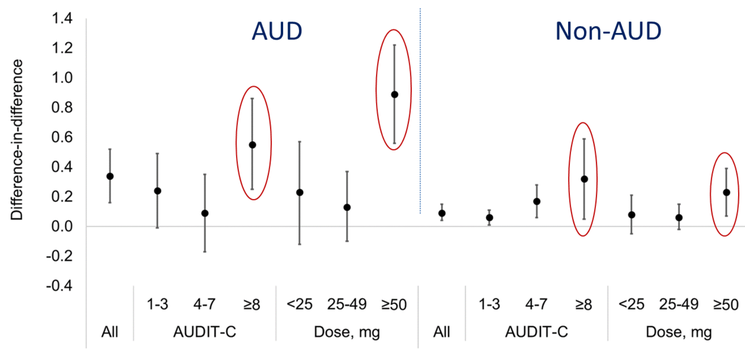


❑ Humans

- **Study 3**: Individuals treated with spironolactone, compared to untreated individuals, showed a greater reduction in number of drinks per week: DID = -0.76 (95% CI = -1.43, -0.11).
- Baseline level of alcohol use was a significant moderator.
- A significant dose-response relationship was found; each additional 10 mg of spironolactone prescribed was associated with a reduction of 0.36 drinks/week.



- **Study 4**: Individuals treated with spironolactone, compared to untreated individuals, showed a greater reduction in AUDIT-C scores: DID (AUD) = -0.34 (95% CI = -0.16, -0.52), DID (non-AUD) = -0.09 (95% CI = -0.04, -0.15).
- Largest effects were observed among individuals with heavy alcohol consumption and daily spironolactone dose of ≥ 50 mg.



CONCLUSION

- Spironolactone administration in rodent experiments, as well as spironolactone prescription in human observational studies, was associated with reduced alcohol consumption.
- MR antagonism, using spironolactone or other compounds, may be further explored as a novel pharmacotherapy for AUD.

Funding:
NIDA ZIA-DA000635 and NIAAA ZIA-AA000218 (PI: LL); NIDA ZIC-DA000602 (PI: GFK); NIAAA RO1-AA023733, U24-AA020794, and U01-AA020790 (PI: ACJ); NIAAA HHSN275201800625P (PI: CW).

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