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NEUROFAN

RPTPβ/ζ INHIBITION REDUCES REPEATED BINGE DRINKING AND MODULATES PERSISTENT PREFRONTAL NEUROIMMUNE ADAPTATIONS

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Background

Adolescence is a critical period for brain maturation in which this organ undergoes key plasticity mechanisms that increase its vulnerability to the effects of alcohol. **Pleiotrophin** (PTN) is a cytokine that modulates ethanol reward and is an endogenous inhibitor of Phosphacan (a.k.a. **RPTPβ/ζ**). This receptor has a crucial role in areas significantly affected by alcohol consumption such as the hippocampus or prefrontal cortex[1]. We previously showed that **MY10**, a small-molecule inhibitor of RPTPβ/ζ[2] reduces ethanol consumption in adolescent mice[3], adult mice[4] and adult rats[5]. We hypothesize that PTN and Phosphacan also play important roles in chronic ethanol consumption and in the cognitive and neural adaptations associated with ethanol during adolescence.

Methods

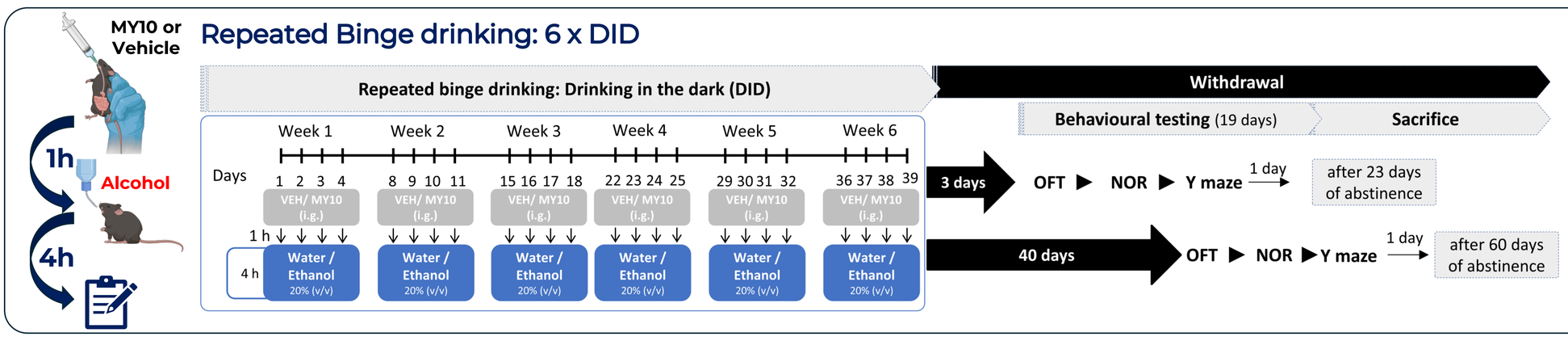

Figure 1. Repeated ethanol binge drinking model. The 4-day drinking in the repeated ethanol binge drinking procedure was performed in mice for 6 weeks. In both models, mice were given 60 mg/kg MY10 or its vehicle (i.g.) 1 h before the access to a 20% ethanol solution in each drinking session. Three or forty days after the last drinking session, mice were subjected to 3 behavioural tests: the Open Field Test (OFT), the Novel Object Recognition Test (NOR) and a reversal learning test (RLT).

Results

1. MY10 decreases ethanol consumption in male and female mice

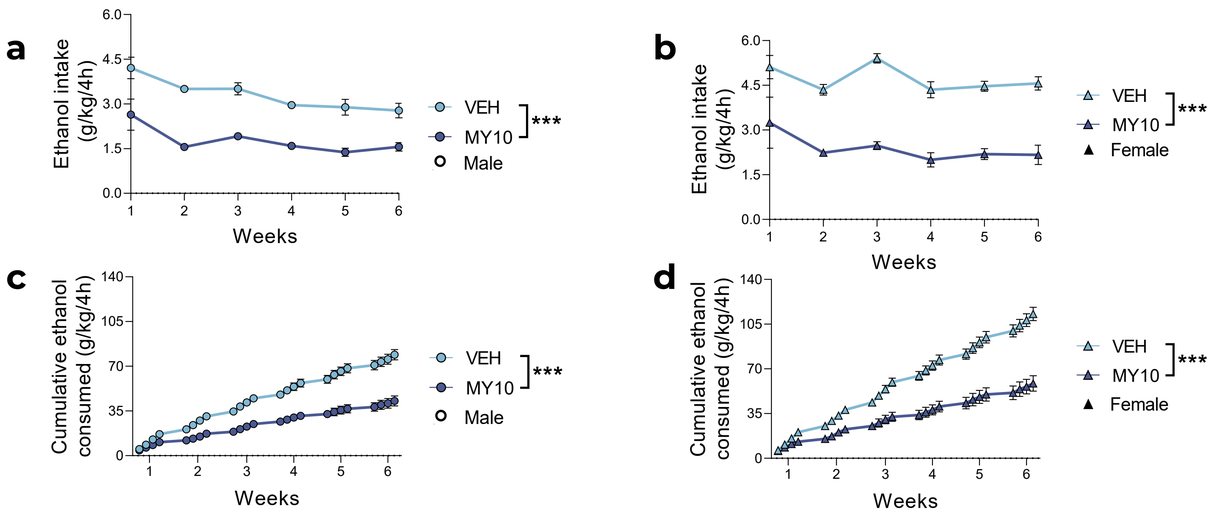

Figure 2. Effects of MY10 treatment in ethanol consumption in the repeated binge drinking procedure. Average 4 h ethanol consumption (in g/kg) in MY10-treated and vehicle (VEH)-treated male (a) and female mice (b). Cumulative ethanol consumption (in g/kg) in MY10-treated and vehicle (VEH)-treated male (c) and female mice (d). Data are presented as mean ± SEM (n = 28-30 animals per group). ***p < 0.001 for differences in treatment

2. MY10 decreases anxiety-like behaviour after 3 and 40 days of ethanol abstinence

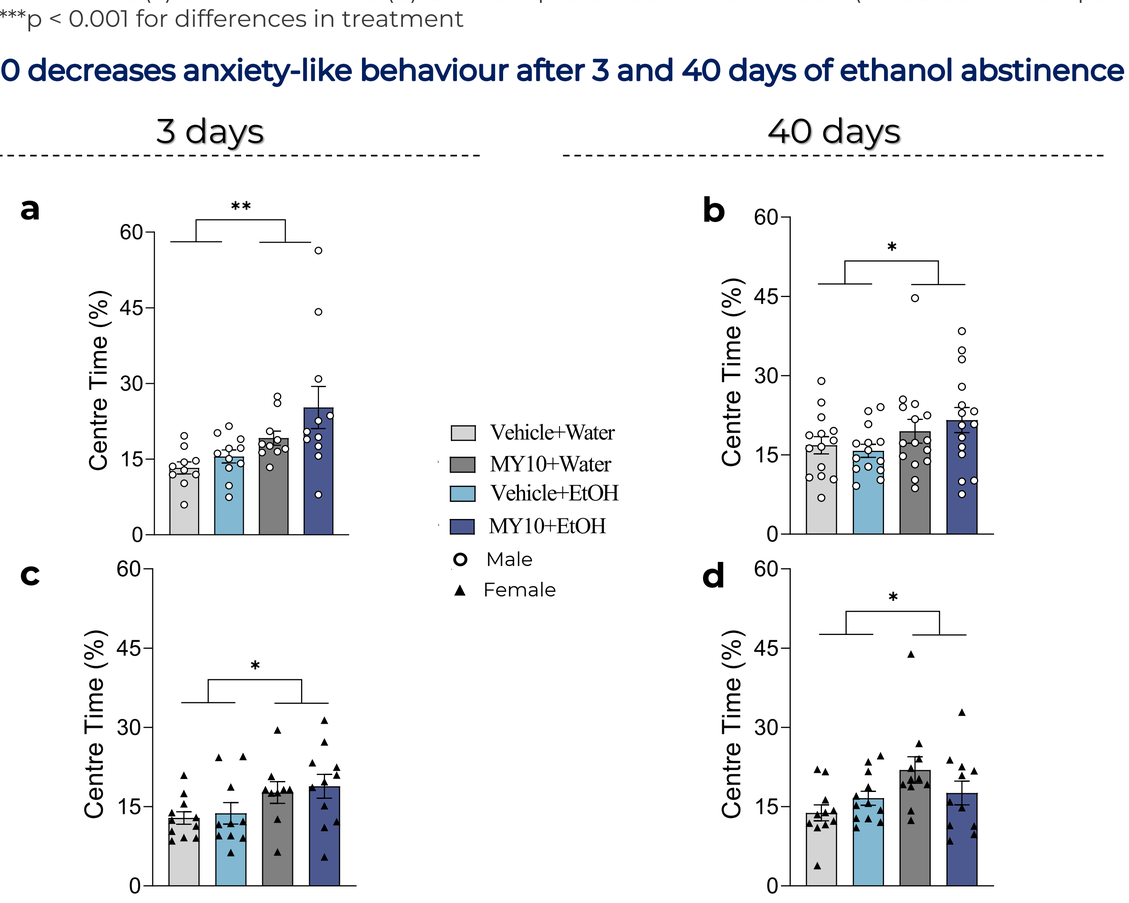

Figure 3. Effect of MY10 on open field test (OFT). Percentage of time spent in the centre zone by adolescent wild type mice exposed to repeated binge drinking protocol. After the consumption protocol, the mice were maintained for 3 (a-b) or 40 days (c-d) previous to behavioral test. Data are presented as mean ± SEM. ** $p < 0.01$; * $p < 0.05$; from two-way ANOVA.

3. MY10 treatment transiently increases cognitive flexibility

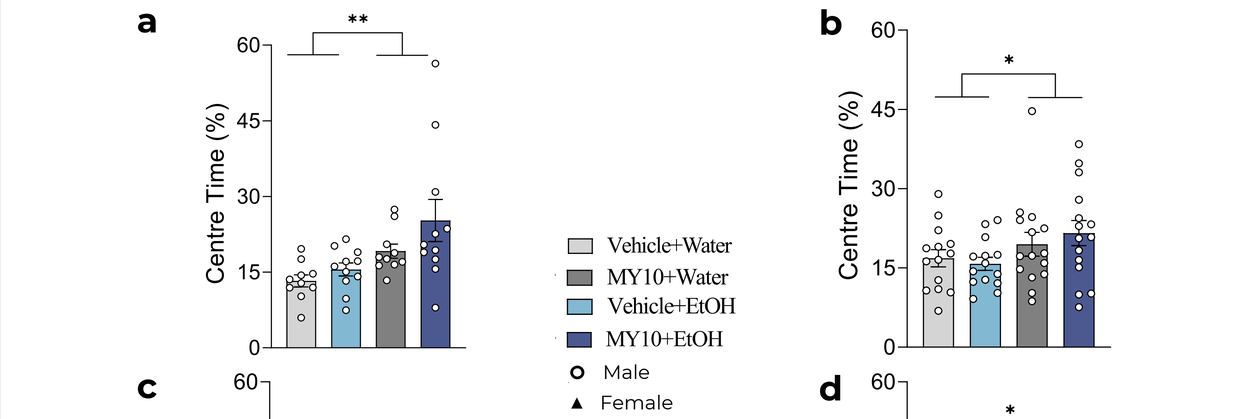

Figure 4. Effect of MY10 on Y maze test. Percentage of time spent in the success arm in learning phase (a) and in reversal learning phase (b) by adolescent wild type mice exposed to repeated binge drinking protocol. After the consumption protocol, mice were maintained for 3 days previous to behavioral test. Data are presented as mean ± SEM. *p < 0.05; from three-way repeated measures ANOVA.

4. Repeated binge drinking and MY10 treatment differentially affect neurotransmission, stress, neuroinflammation, and PNN markers in the mouse PFC

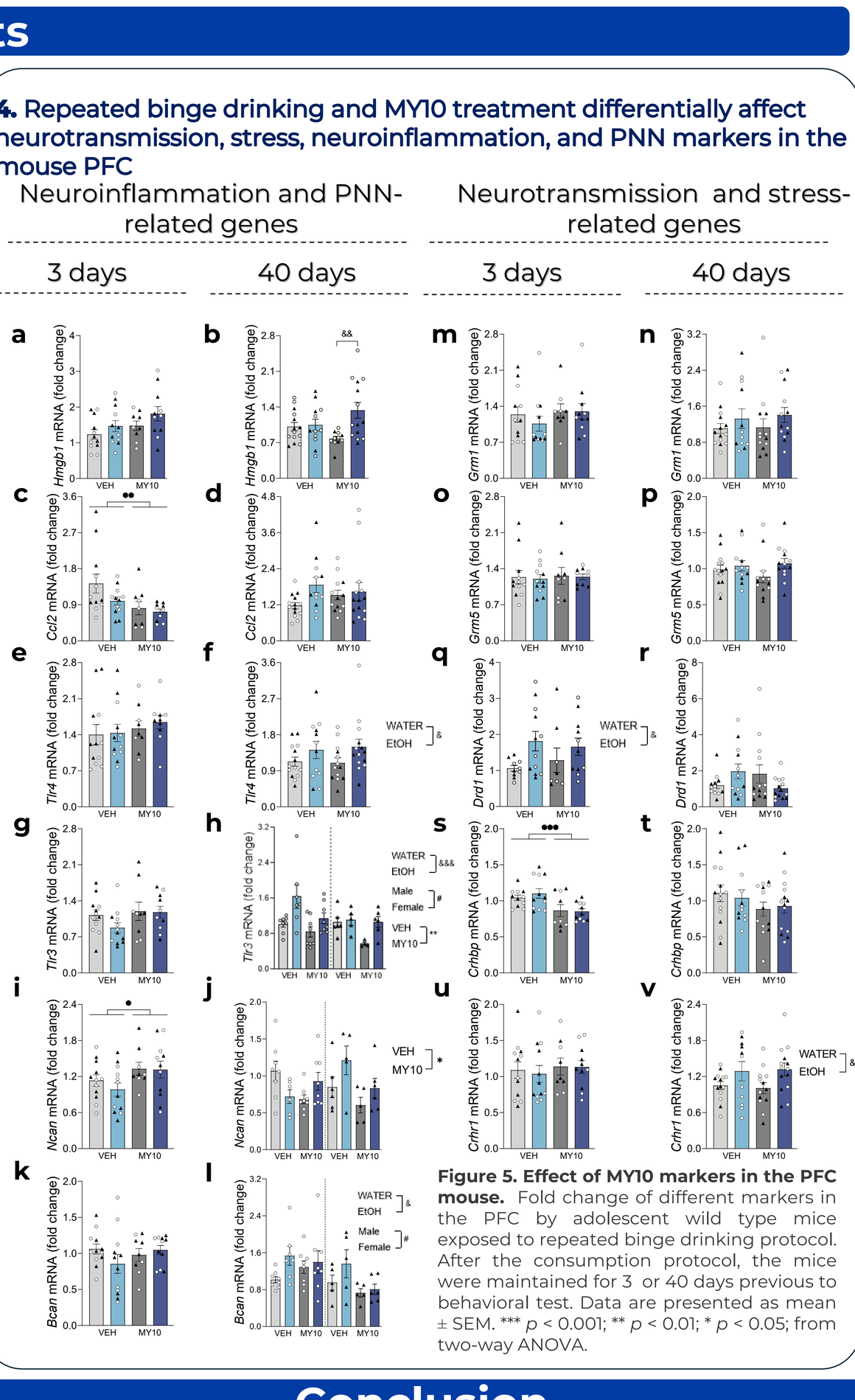

Figure 5. Effect of MY10 markers in the PFC mouse. Fold change of different markers in the PFC by adolescent wild type mice exposed to repeated binge drinking protocol. After the consumption protocol, the mice were maintained for 3 or 40 days previous to behavioral test. Data are presented as mean ± SEM. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; from two-way ANOVA.

Conclusion

The data indicate that RPTPβ/ζ inhibition reduces repeated binge-like ethanol consumption, induces persistent OFT behavioural changes consistent with reduced anxiety-like behaviour, modifies task-related behaviour in a rewarded Y-maze, and alters long-term TLR-related transcriptional responses in the PFC.

Acknowledgements

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DELEGACIÓN DEL GOBIERNO PARA EL PLAN NACIONAL SOBRE DROGAS
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