Downregulation of Clock Genes in the Accumbal Shell Reduces Binge Drinking in Mice.

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INTRODUCTION

- Binge drinking is a common and deadly pattern of alcohol abuse that is responsible for more than 50% of alcohol related deaths.
- Preclinical studies suggest that clock genes responsible for circadian rhythm are strongly associated with alcohol abuse and binge drinking
- The shell region of Nucleus accumbens (NAcSh) is particularly important for reward and addiction including binge drinking.
- Clinical and preclinical studies strongly suggest that circadian clock disruption increases alcohol drinking

Question

Is alcohol consumption associated with an increased expression of major circadian genes (Clock, Per1 and per2)?

Will antisense-induced downregulation of these genes in the NAcSh reduce binge drinking?

Conclusion

Clock genes in the NAcSh play a crucial role in binge drinking

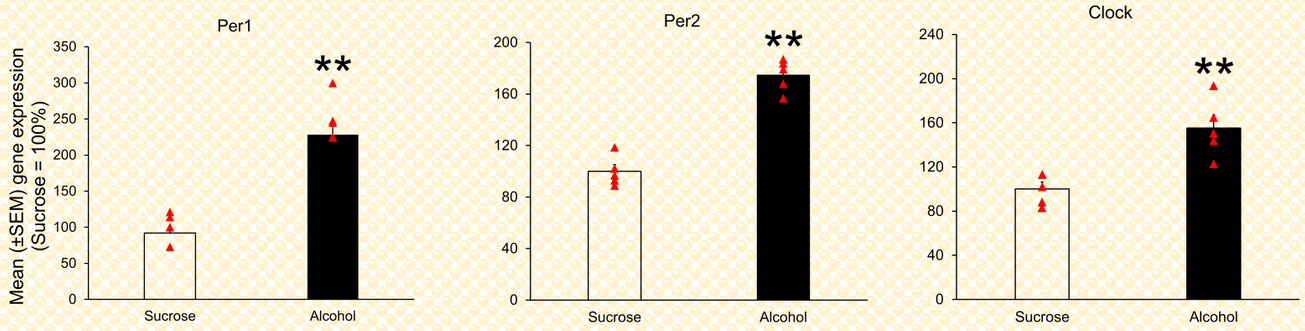
Findings

Binge drinking is associated with increased expression in circadian genes in the NAcSh but not in the SCN

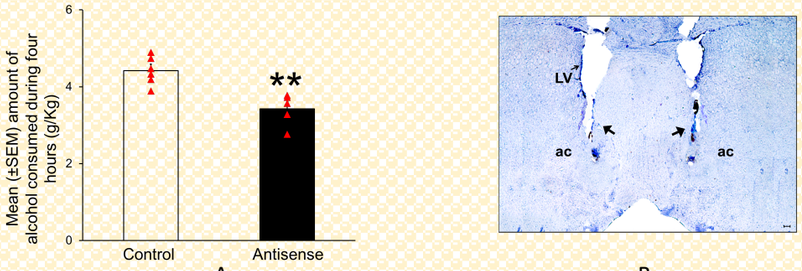
Antisense-induced downregulation of circadian genes in the NAcSh reduces alcohol consumption but has no effect on water and sucrose consumption

RESULTS

Alcohol consumption increases expression in circadian genes



Antisense induced downregulation



A B

(A) Mice in the Antisense group showed significant reduction in alcohol consumption
(B)Photomicrograph depicting bilateral injection sites in the NAcSh

METHODS

Experiment 1

Animals: C57BL/6J mice; **Surgeries**: None; **Alcohol/Sucrose consumption**: Using Drinking in Dark (DID) paradigm, animals were exposed to alcohol (20%) /sucrose (10%) for 2 hours on Days 1-3 and for 4 hours on Day 4. **Circadian Gene expression**: After 4 hours of alcohol/sucrose consumption, animals were euthanized and their brain isolated, NAcSh and SCN dissected out and processed for RT-PCR.

Experiment 2

Animals: C57BL/6J mice; **Surgeries**: Implantation of bilateral guide cannula above the NAcSh; **Alcohol/Sucrose/water consumption**: As in Experiment 1; On Day 4, one hour prior to the onset of alcohol/sucrose/water exposure, mice were bilaterally infused with either a mixture of Clock, Per1, and Per2 antisense oligodeoxynucleotides (AS-ODNs; Antisense group) or nonsense/random ODNs (R-ODNs; Control group) into the NAcSh. Blood alcohol concentration was measured to confirm binge drinking. Microinfusion sites were histologically verified using cresyl violet staining.