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Constant light exposure in mice potentiates ethanol consumption and preference and disrupts circadian locomotor activity rhythms

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CONSTANT LIGHT EXPOSURE IN MICE POTENTIATES ETHANOL CONSUMPTION AND PREFERENCE AND DISRUPTS CIRCADIAN LOCOMOTOR ACTIVITY RHYTHMS

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INTRODUCTION

Single-nucleotide polymorphisms of *mPer2* have recently been implicated in predisposition for alcohol abuse and alcoholism. We and others have shown that constant light exposure (LL) attenuates the circadian expression of *mPer2* within the mammalian circadian pacemaker and depresses circadian activity rhythms. These experiments exploit this suppressive effect of LL on *mPer2* and circadian activity as a physiological approach to explore the etiology of alcohol abuse and alcoholism in the male C57BL/6J mouse.

METHODS

Ethanol Treatment. Male mice (n=11) were given a choice between a 15% ethanol solution (vol/vol) or tap water. Ethanol consumption was measured daily to the nearest 0.25 mL in 50 mL graduated tubes at the beginning of the dark phase (active period) of a 12L:12D photocycle (LD). Position of the drinking bottle was controlled. An ethanol preference ratio was calculated: (daily ETOH consumption/daily total fluid consumption).

Photocycle. The experiment was divided into two phases; *Phase 1:* Mice were housed under LD for 2 wks. *Phase 2:* Mice were released to constant light (270 lux) for the remaining 2 wks. General circadian locomotor activity was measured using a passive infrared motion detector interfaced to a computerized data acquisition system.

Circadian Measures. The period (tau) of circadian activity rhythms was calculated using a least-squares regression line through a minimum of seven daily activity onsets. Activity onset was characterized as the initial period of activity that 1) exceeded 10% of the maximum rate for the day; 2) was preceded by at least 4 hr of activity quiescence; and 3) was followed by at least 60 min of sustained activity. The temporal structure of circadian locomotor activity was assessed through quantifying activity bout number and duration across the 24 hour circadian day. An activity bout was defined by a > 1 min activity period separated by at least 10 min of inactivity.

RESULTS

Constant Light Exposure Potentiates Ethanol Consumption and Preference. Mice consumed significantly more ethanol under LL vs. LD (21 +/- 5 g/kg vs. 14 +/- 3 g/kg, respectively; p<0.01). Treatment differences were observed on days 3, 4, and 12. Preference for ethanol was greater under LL vs. LD (30 +/- 1% vs. 20 +/- 1%, respectively; p<0.01). Treatment differences were observed on days 3, 4, and 11. A positioning effect was also observed; preference for ethanol was greater on the left vs. right (24 +/- 1 % vs. 21 +/- 1 %, respectively; p<0.04; **Fig. 1**).

Constant Light Exposure Severely Disrupts Circadian Locomotor Activity Rhythms. Rhythm period was significantly lengthened under LL (25.00 +/- 0.1 hr vs. 24.00 +/- 0.1 hr for LD; p<0.01). LL increased intermittent, sporadic circadian locomotor activity, reflected through increased bout quantity of reduced duration (quantity: 21.7 +/- 0.8 vs. 14.3 +/- 0.4 for LD; duration: 19.9 +/- 1.5 vs. 52.1 +/- 3.4 min for LD; both p<0.01; **Fig. 2 and 3**).

CONCLUSIONS

1. Long-term constant light exposure (LL) potentiates ethanol consumption and preference
2. Potentiated ethanol consumption and preference is concomitant with severe LL-induced disruptions of circadian locomotor activity rhythms
3. These effects occur in tandem with decreased *mPer2* expression shown previously, and thus LL may be useful for further studies of alcohol abuse and alcoholism.

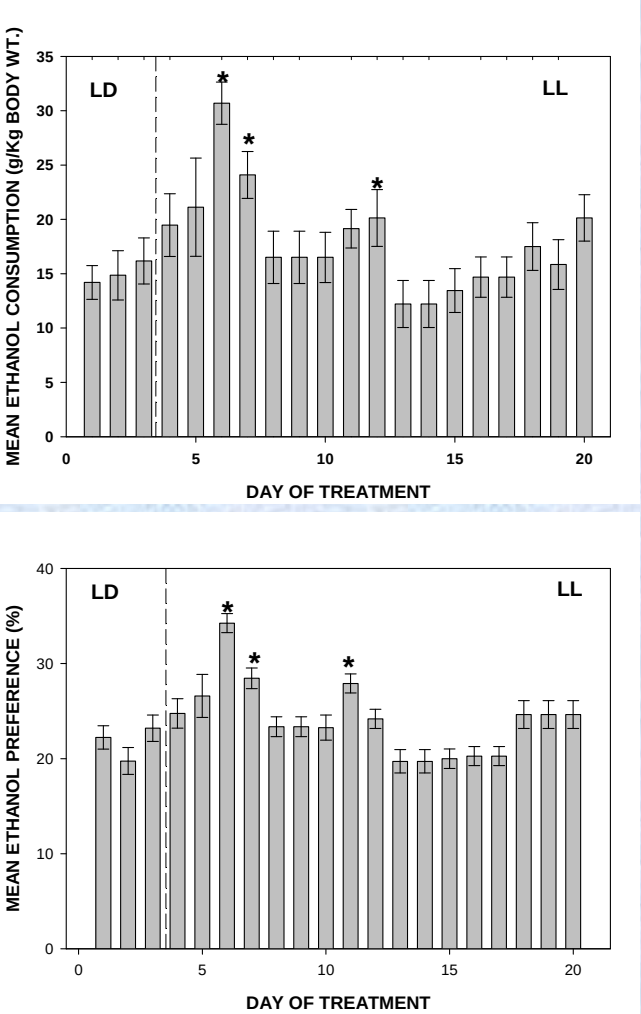

Figure 1: Ethanol consumption (top) and preference (bottom) with respect to photocycle (LD; 12L:12D photocycle: LL; constant light) are shown. Constant light exposure augmented ethanol consumption and preference. Asterisks annotate day of treatment effects (p<0.05).

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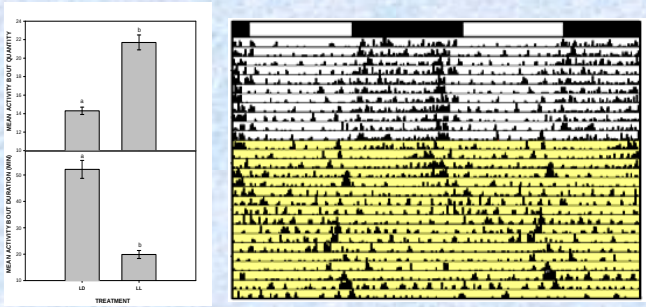
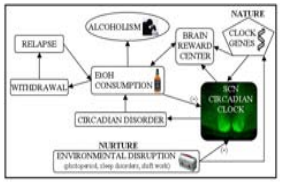
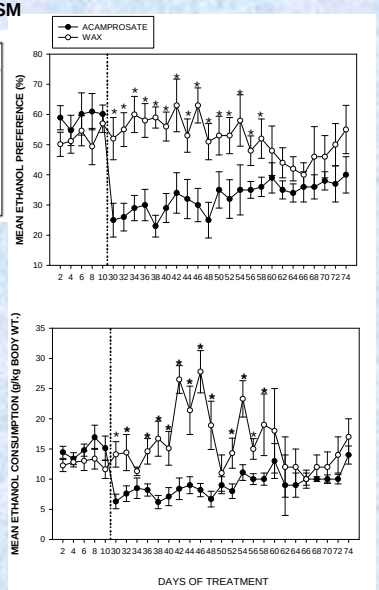


Figures 2 and 3: Representative, double-plotted actogram of general circadian locomotor activity (right). Shaded yellow demarcates constant light exposure (LL). White and black bars represent light and dark periods under a standard 12L:12 D photocycle, respectively. As illustrated, constant light altered the robustness of circadian locomotor activity rhythms by means of lengthening tau and increasing intermittent, sporadic activity (left) reflected through increased activity bout quantity of reduced duration. These chronobiological disturbances under LL were concomitant with increased ethanol consumption and preference.

FUTURE DIRECTIONS: ENVIRONMENTAL AND GENETIC CIRCADIAN INFLUENCES ON ALCOHOLISM



Schematic annotates the broad influence the environment and clock genes have on circadian clock timing and alcohol addiction and reward. As shown, residual environmental disruptions such as repeated jet lag and rotating shift work disrupt clock gene expression and subsequent circadian clock function, These physiological perturbations facilitate self-medicating with alcohol in an attempt to mitigate sleep/wake disturbances and thus, create a vicious cycle of alcohol dependence and chronobiological disruption.



Ethanol consumption (top) and preference (bottom) for a 15% ethanol solution or water were measured before (baseline) and after (re-introduction) bilateral implantation of acamprosate (300 mg/g wax) or blank wax pellets into the ventral tegmental area (VTA) of the pons. The dotted-line annotates the 3 wk period of ethanol withdrawal preceding ethanol re-introduction. Relative to baseline, acamprosate implantation into the VTA significantly reduced ethanol consumption (8 g/kg vs. 13 g/kg for baseline; p<0.05) and preference (25% vs. 56% for baseline; p<0.05).