Rapid development of tolerance to the sleep promoting effects of alcohol-A mouse model

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Background & Significance

Alcohol and Tolerance

- Tolerance is defined as an accentuated reduction of alcohol's effect with the constant use of the same quantity.
- Alcohol tolerance is characterized as acute, rapid and chronic;

Acute tolerance develops within a single exposure session,
Rapid tolerance within 8-24 hr after the first exposure, and importantly, it predicts chronic tolerance.
Chronic tolerance occurs with repeated exposures over days or weeks

Alcohol tolerance and Sleep

- Alcohol promotes sleep and widely used as a sleep aid.
- Tolerance to the sleep promoting effects of alcohol develops over time with its repeated use which plays an important role in gradual escalation of alcohol consumption resulting in alcohol dependence.
- To understand the mechanism underlying alcohol tolerance and dependence, it is required to have an appropriate model mimicking human conditions of alcohol administration and development of tolerance to the sedative effects of alcohol.

We propose an animal model which closely mimics human conditions of alcohol self-administration with a clear demonstration of rapid tolerance to the sedative effects of alcohol

Methodology

- Animal: Male C57BL/6J mice were used. The advantage of using these animals in sleep experiments is that they are genetically prone to self-administer alcohol to a level of intoxication. So, no stressful animal handling is required to administer alcohol which may affects their sleep.
- Surgery: Under standard surgical conditions, mice were implanted with sleep recording electrodes and allowed to recover from surgical stress.
- Alcohol self-administration (4 hr in the dark): After habituation with the sleep recording set up, the experiment was initiated 2.5 hr after the dark onset with water deprivation for 30 min (to instigate alcohol drinking) followed by exposure to pre-weighed sipper-tubes containing 20% alcohol (v/v). After 4 hr, alcohol tubes were removed from the mice cages, weighed and replaced with water containing tubes. Alcohol consumption was calculated and expressed in g/Kg. The detailed protocol is as follows:

  Baseline day (BL): Water deprivation only (30 min),

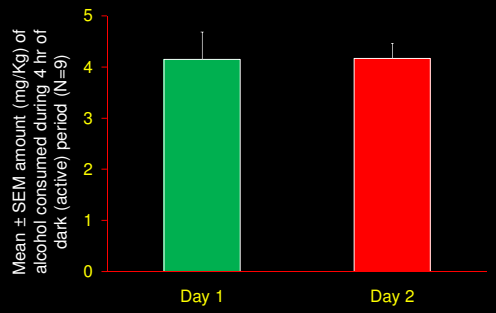
  Day 1: Water deprivation (30 min) + 4 hr alcohol self-administration;

  Day 2: Same as on Day 1
- Sleep-wake behavior [Wakefulness, non-rapid eye movement (NREM) and rapid eye movement (REM) sleep] was recorded starting from the baseline day.
- Blood alcohol concentration (BEC) was measured in a separate group of animals to avoid sleep disturbances during blood sampling.

Results

Alcohol consumption

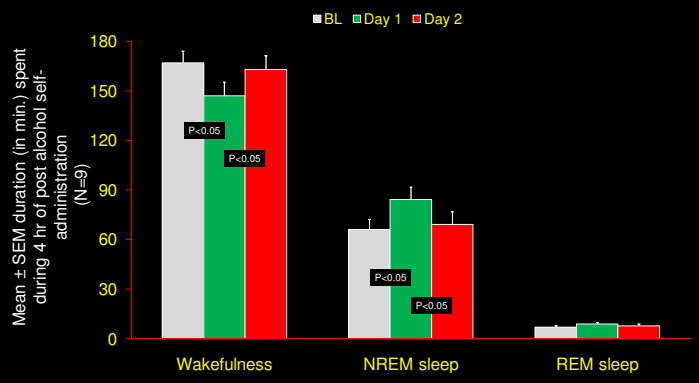
- Mice displayed similar alcohol consumption during 4 hr of alcohol exposure on day 1 and day 2.



Changes in sleep-wakefulness

During 4 hr post-drinking session

- On Day 1, NREM sleep was significantly enhanced with a reduction in wakefulness as compared to the BL.
- On Day 2, wakefulness was significantly enhanced with a reduction in NREM sleep as compared to day 1.
- No change was found in REM sleep on day 1 and 2.



Salient findings

During post-drinking session (4 hr)

- On day 1, mice displayed a robust sleep induction effect as revealed by increased NREM sleep with a concomitant reduction in the wakefulness following alcohol self-administration.
- On day 2, mice showed a significant reduction in sleep promoting effects of alcohol, although, the alcohol consumption was similar to day 1.

Blood alcohol concentration (BEC)

- To determine if reduction in sedative effects of alcohol on day 2 is not due to altered alcohol metabolism, we analyzed BEC in separate group of animals. No change in BEC was observed between day 1 and day 2.

Conclusions

This is the first study to show a mice model of rapid tolerance to the sleep promoting effects of alcohol using a stress-free method of alcohol self-administration closely mimicking alcohol consumption in humans.