



Research report

Chronic alcohol treatment in rats alters sleep by fragmenting periods of vigilance cycling in the light period with extended awakenings

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ABSTRACT

Studies have shown that disturbed sleep produced by chronic alcohol abuse in humans can predict relapse drinking after periods of abstinence. How alcohol produces disturbed sleep remains unknown. In this study we used a novel analysis of sleep to examine the effects of alcohol on sleep patterns in rats. This analysis separates waking into multiple components and defines a period labeled vigilance cycling (VC) in which the rat rapidly cycles through various vigilance states. These VC episodes are separated by long duration wake (LDW) periods. We find that 6 weeks of alcohol (6% in a liquid diet) caused fragmentation of extended VC episodes that normally occur in the light period. However, total daily amounts of slow-wave sleep (SWS) and rapid-eye movement sleep (REMS) remained constant. The daily amount of wake, SWS, and REMS remained constant because the alcohol treated rats increased the amount of VC in the dark period, and the sleep nature of VC in the dark period became more intense. In addition, we observed more wake and less REMS early in the light period in alcohol treated rats. All effects completely reversed by day 16 of alcohol withdrawal. Comparison of the effects of chronic alcohol to acute alcohol exposure demonstrated the effects of chronic alcohol are due to adaptation and not the acute presence of alcohol. The effects of chronic alcohol treatment in rats mimic the effects reported in humans (REMS suppression, difficulty falling asleep, and difficulty remaining asleep).

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1. Introduction

Although acute alcohol is a soporific agent, a frequent complaint of alcoholics is disturbed sleep. Specifically, alcoholics entering rehab programs have been found to have high pressure for rapid-eye movement sleep (REMS), an increase in sleep onset latency, and inability to maintain sleep through the night [3,19,22]. Although REMS returns to normal after cessation of drinking, the insomniac effects can remain for years after recovery [1,5,8,12,13,34,39]. Furthermore, disturbances in sleep patterns in recovering alcoholics have been found to predict the probability of relapse drinking [4,6,8,12,13]. Why disturbed sleep should predict relapse to further alcohol consumption remains unknown, but at an even more fundamental level, the mechanistic basis for disturbed sleep patterns produced by alcohol exposure also remains unknown. An animal model of altered sleep induced by chronic alcohol would be helpful in addressing this issue.

A common animal model for both sleep and alcohol research is the rat. However, a difference between rat and human sleep is that rats are polyphasic sleepers whereas humans are monophasic sleepers. Thus when human alcoholics (or recovered alcoholics) complain of failure to maintain sleep throughout their monophasic sleep period, it becomes difficult to assess this parameter in the rat since rats normally have frequent awakenings throughout the rest period. Recently we developed an analysis of sleep patterns in rats that separates wake episodes into brief wake (BW) and long duration wake (LDW), and we used this division to identify a sleep unit that occurs between LDW events [33]. The term vigilance cycling (VC) was used as the label for this sleep period because of the rapid cycling between different vigilance states. In our prior study we suggested that periods of VC are analogous to the 8-h monophasic sleep period in humans. In the present study we used this analysis to examine the effects of chronic and acute alcohol consumption on sleep in rat.

We found that the long periods of VC that normally occur in the light period in untreated rats are fragmented into shorter periods by the chronic alcohol treatment. Further, since slow-wave sleep (SWS) and REMS occur within VC periods, there is also a drop in the overall amount of SWS and REMS in the light period. On the other hand, during the dark period VC takes on the more sleep intensive appearance of VC in the light period such that daily amounts of SWS

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and REMS are not altered by the chronic alcohol treatment. These effects of chronic alcohol are not mimicked by acute exposures to alcohol. These results document that the effects of chronic alcohol in rat (fragmentation of prolonged sleep episodes and suppression of REMS in the light period) are a result of adaptations to the presence of alcohol and closely resemble the pathologies observed in human alcoholics.

2. Methods

2.1. Chronic alcohol treatment

Sixteen male Sprague-Dawley rats (250–275 g at the beginning of the treatment) were used; eight of them were assigned to the alcohol treated group and eight to the pair-fed control group. Beginning body weights were matched between the two groups. Rats were housed individually at $22 \pm 2^\circ\text{C}$ ambient temperature with a 12 h:12 h light:dark cycle. Alcohol treated rats were treated with 6% alcohol (grain alcohol, Everclear) in liquid diet (Bio-serv) for 6 weeks. The alcohol treated rats consumed on average 11 ± 0.2 g alcohol/kg body weight/day. In a prior study we found that this protocol produces a blood alcohol level of $\sim 0.12\%$ when blood samples are taken at the end of the dark period [18]. Each pair-fed rat was given alcohol-free liquid diet of equal caloric content (calories from alcohol replaced with maltose dextrin) to that consumed by the weight-matched alcohol treated rat. All rats had *ad lib* access to water. These rats are the same rats for which previous results have been reported [23]. The focus of this previous study was to determine the optimum treatment protocol to produce alcohol-induced changes in sleep patterns. The results contained within the present report are a more detailed analysis from this group of animals and includes the data from the recovery period after cessation of alcohol treatment.

2.2. Acute alcohol treatment

Twenty male Sprague-Dawley rats (approximately 350 g) were used for dark onset alcohol administration study and 19 rats of similar specifications for light onset alcohol administration. Housing, ambient temperature and light cycles used in these experiments were the same as described in the chronic alcohol treatment study. Alcohol (Everclear) was administered within 30 min prior to a scheduled light change in a 30% solution in tap water (1 ml/100 g body weight) by gastric gavage (final dose 2.4 g/kg body weight). Control recordings were obtained after an equivalent water gavage (1 ml/100 g body weight). Rats had *ad lib* access to food and water at all times. Administration of alcohol at 3 g/kg produces a blood alcohol level around 0.153% after 90 min and 0.1% at 3 h [37].

All experiments were done with the approval of the institutional animal care and use committee of Washington State University.

2.3. Instrumentation for sleep recordings

Surgical implantation of permanent EEG and EMG electrodes was as described previously [23]. A week of recovery from the instrumentation was allowed before sleep recordings commenced. In the chronic treated animals the instrumentation was done during the 5th week of the alcohol exposure. The alcohol diet was continued during the time of instrumentation.

2.4. Sleep recordings

During the period of data collection sleep recordings were made in enclosed environmental chambers as described previously [23]. Alcohol and pair-fed treatments continued in the environmental chambers through the first 2 days of sleep recordings after which the alcohol was removed from the diet of the alcohol treated animals over a 2-day period (6% to 3% to 0%). Recordings were interrupted for 1 h each day (last hour of light period) for animal care. However since we analyze data in 2 h blocks we excluded data in the last 2 h block in the light period. After weaning from alcohol, the liquid diet was continued and additional sleep recordings were collected periodically throughout the recovery period. In the present study we report findings from recordings on the last 6% alcohol day and those obtained 2 days and 16 days after termination of the alcohol treatment. In the acute alcohol studies the animals were also gavaged daily during the 3-day habituation period.

2.5. Collection and analysis of EEG and EMG signals

We collected and analyzed the EEG and EMG signals as described previously [33] using an 8-s epoch in the primary analysis of the sleep records. A 300 s cutoff was used to separate BW from LDW. VC events were those events between LDW episodes. Further, as described previously [33] any isolated SWS events that were surrounded by LDW were not considered VC (because no cycling occurred), and such events were not used to divide periods of LDW. When examining the variation in slow-wave amplitude (SWA; average of amplitudes in the 0.5–4 Hz frequency bands

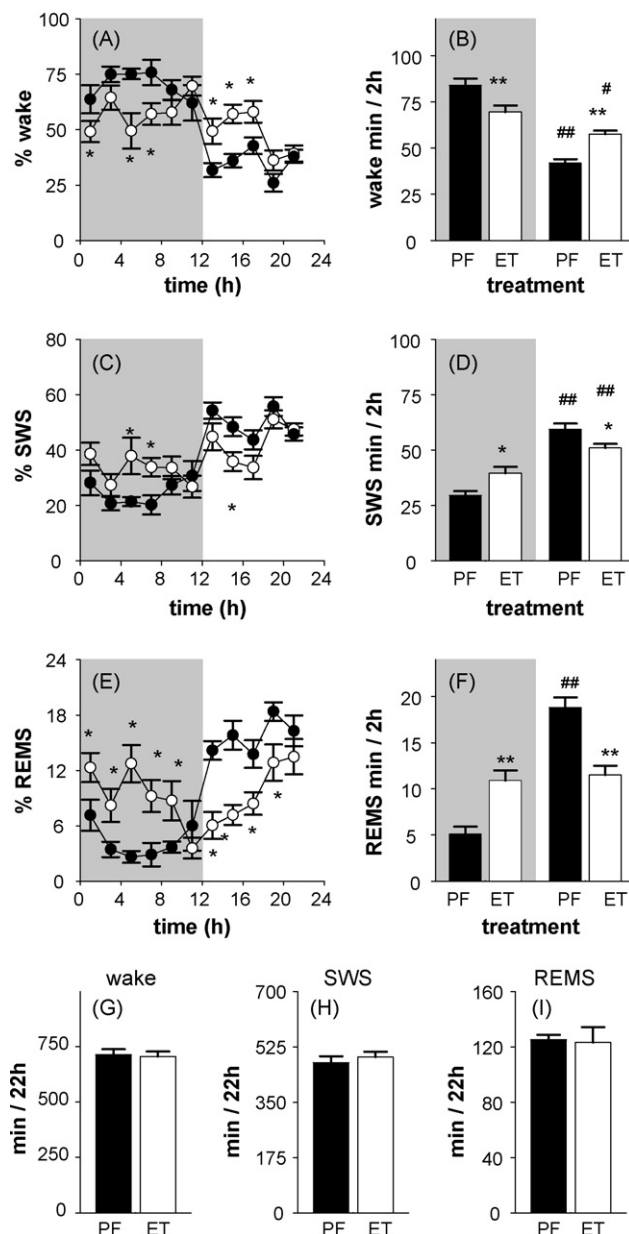


Fig. 1. Vigilance state diagram for alcohol treated (open symbols and bars; $n=8$) and pair-fed (filled symbols and bars; $n=6$) rats after 6 weeks of alcohol treatment. In this and all subsequent graphs shaded portion of graphs indicates dark period and unshaded area light period. Panels (A), (C), and (E) indicate percent of time spent in indicated vigilance state in 2-h time blocks. Panels (B), (D), and (F) summarize the distribution of vigilance states across dark and light periods. Panels (G), (H), and (I) illustrate the total amount of each vigilance state across the entire 22 recording period. Asterisks indicate that the alcohol treated value is statistically different from pair-fed value at the same time ($*p < 0.05$, $**p < 0.005$). Pound signs indicate the light period value is significantly different from the corresponding dark period value within the treatment group ($\#p < 0.05$, $##p < 0.005$).

only during SWS episodes) across the 22 h of recording, we averaged the SWA across the entire recording for each rat, and then the average SWA within each 2-h block was expressed as a percentage of the average across the entire recording.

2.6. Statistical analysis

In the course of the experiment the instrumentation on two pair-fed animals failed before the first sleep recordings were made at the end of the alcohol treatment period. Thus the results reported from this phase of the treatment are from eight alcohol treated animals and six pair-fed animals. During the recovery period (after day 2), the instrumentation on two of the alcohol treated animals

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