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Acute binge alcohol administration reverses sleep-wake cycle in Sprague Dawley rats

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Abstract

Background—Binge alcohol drinking is amongst the most common pattern of alcohol consumption in our society. Binge alcohol consumption has serious negative consequence on mental and physical health. Although alcohol consumption is known to have profound impact on sleep, it is yet unknown as to how binge alcohol affects/alters sleep-wakefulness. The objective of this study was to examine the effect of acute binge alcohol administration on sleep-wakefulness.

Methods—Male Sprague-Dawley rats were used in the study. Under standard aseptic surgical conditions, rats (N=7) were implanted with sleep recording electrodes. After post-operative recovery and habituation, baseline sleep-wakefulness was recorded. Subsequently, rats were exposed to binge alcohol treatment as follows: One hour before light onset, a priming dose of 5 g/Kg of alcohol was administered followed by two subsequent doses (adjusted based on the intoxication level of the rat) approximately 8 hours apart. Sleep-wakefulness was continuously recorded for three days post-binge.

Results—Acute binge alcohol administration had no significant effect on sleep-wakefulness on post-binge Day 1. However, on post-binge Day 2, after blood alcohol concentration was zero, sleep disruptions were observed manifested by a reversal of sleep-wakefulness as evident from insomnia-like symptoms (significant increase in wakefulness; significant reduction in NREM sleep) during the normal sleep (light) period and excessive sleep (significant increase in NREM sleep) during the normal active (dark) period similar to excessive daytime sleepiness in humans. All sleep-wakefulness changes were normalized on day 3 post-binge.

Conclusions—Alcohol hangover is defined as the presence of unpleasant symptoms that peak when blood alcohol concentration is zero. Our results suggest that the reversal of sleep-wakefulness accompanies alcohol hangover after binge alcohol administration.

Keywords

Binge; Rat; Sleep; Hangover

INTRODUCTION

Alcohol is the most commonly abused drug worldwide and the leading cause of preventable death in our society (Rehm et al., 2009; Shield et al., 2013). Alcohol abuse entails several maladaptive patterns of alcohol consumption; however, the most harmful and common among all age groups is the “Binge” pattern (Centers for disease Control and Prevention (CDC), 2012; Naimi et al., 2010; Naimi et al., 2003). While there is some confusion regarding the definition of binge alcohol drinking (Herring et al., 2008), it is generally accepted that binge drinking is a pattern of alcohol drinking whereby large volumes of alcohol are consumed on a single occasion resulting in high (>80 mg/dL) blood alcohol concentrations (Herring et al., 2008; NIAAA, 2004; Gmel et al., 2011; Wechsler et al., 1994). This binge pattern of drinking is associated with high risk for the development of alcohol dependence (Courtney and Polich, 2009; Knight et al., 2002). Out of an estimated 80,000 deaths caused by alcohol abuse in an year, binge drinking accounted for more than half of the deaths (Centers for disease Control and Prevention (CDC), 2012; Bouchery et al., 2011; Centers for disease Control and Prevention (CDC), 2004). Moreover, binge drinking, especially in very infrequent drinkers (binge drink once in a year or less), is amongst the most important predictors of injury, morbidity, and mortality risks (Taylor et al., 2008; Vinson et al., 2003; Gmel et al., 2011).

Sleep disruptions are amongst the most common and severe consequences of alcohol consumption. Sleep disruptions affect multiple behaviors which are critical for social and academic competence including performance, learning and emotional stability (Kamphuis et al., 2012; Roehrs and Roth, 2001a). Most importantly, sleep disruptions including insomnia and daytime sleepiness are positively associated with chronic binge drinking and are considered as risk factors for substance use and alcohol-related problems (Shibley et al., 2008; Brower, 2001; Brower et al., 2001; Popovici and French, 2013). How does acute binge alcohol drinking affect sleep? While sleep-wakefulness following acute and chronic alcohol intake, and tolerance development to the sleep promoting effects of alcohol has been examined, the effect of acute binge alcohol consumption on sleep-wakefulness has never been examined (Sharma et al., 2010; Sharma et al., 2013a; Sharma et al., 2013b; Thakkar et al., 2010b). Hence, this study was designed to examine whether binge alcohol administration affects sleep-wakefulness. Our hypothesis was that binge alcohol administration will have profound effect on sleep-wakefulness.

MATERIALS AND METHODS

All animal experiments were performed according to the American Association for Accreditation of Laboratory Animal Care’s policy and Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research. All protocols were approved by Animal’s Committee of the Harry S. Truman Memorial Veterans Hospital.

Animals

Male Sprague-Dawley rats (250–300 g) were obtained (Charles River, Wilmington, MA, USA) and housed under 12–12 hour light-dark cycle [lights-on (ZT0) at 10 AM] with ambient room temperature (25°C) and ad libitum access to food and water. Rats were

allowed to recover from transportation stress and allowed to acclimatize with the new environmental conditions for at least 7 days.

Surgery

Under sterile surgical conditions and under inhalation anesthesia (1% isoflurane), rats were implanted with sleep recording electrodes as previously described (Sharma et al., 2013b; Thakkar et al., 2003; Thakkar et al., 2001). In brief, bilateral screw electrodes were implanted on the skull to record the electroencephalogram (EEG). Three flexible stainless steel loops were fixed onto the superior nuchal muscles for recording electromyogram (EMG). One indifferent electrode (ground) was implanted on one side of the nasal suture. All electrodes were connected to a six channel electrode pedestal (MS363, Plastics One Inc, Roanoke, VA) and fixed on the skull by acrylic cement.

Post-operative recovery and habituation

Experiments were conducted with the same light conditions as described above and with food and water available *ad libitum*. After surgery, the animals were singly housed in sleep recording cages (similar to normal rat shoebox cages, except taller). After 3 days of post-operative recovery, rats were tethered to a lightweight recording cable and allowed to habituate to the recording setup for 5–7 days.

Baseline sleep-recording Day

Once the animals were habituated, the experiment was begun by electrographic recording of baseline sleep-wakefulness for 23 hours, ending one hour before light onset on binge alcohol treatment day.

Binge alcohol treatment Day

Animal studies suggest that to mimic “binge” effects in animals, multiple alcohol exposures are required (Courtney and Polich, 2009). Thus, we used a truncated version (one day) of Majchrowicz’s binge alcohol administration protocol as described previously (Majchrowicz, 1975; Faingold, 2008; Sharma et al., 2010). We chose this protocol because it resembles the route of alcohol intake in humans, the degree of alcohol intoxication achieved during binge-drinking episodes, and results in blood alcohol concentration (BAC) in the range of those reported in trauma patients in emergency rooms across the United States [see (Greiffenstein et al., 2007; Courtney and Polich, 2009; Sprow and Thiele, 2012)] In brief, after 23 hour of baseline sleep-wakefulness recording, rats were untethered and a 5 g/kg priming dose of alcohol [35% alcohol (v/v; 200 proof; Fisher Scientific) containing infant formula (8.5%; PBM Nutritionals, Georgia VT)] was administered intragatically (ig) (Sharma et al., 2010). Subsequently a second dose of alcohol was administered seven hours later followed by a third dose eight hours after the second dose (15 hours after the first dose). The doses of alcohol were adjusted based on the intoxication level. The level of intoxication was assessed by placing the animal on a flat surface and observing its behavior for 2 min as described in Table 1 (Majchrowicz, 1975; Sharma et al., 2010; Thakkar et al., 2010a). We did not perform any sleep recording on binge alcohol treatment day because recording cables interfered with inadvertently assumed positions of intoxicated animals. The animals were

reconnected back to the recording cable only after they appeared minimally intoxicated and displayed ambulatory behavior (approximately nine hours after the last dose of alcohol).

Post-binge Days

Post-binge sleep-wakefulness recording was commenced at light onset on post-binge Day 1 and continued until the end of dark period on post-binge Day 3.

Sleep-wakefulness analysis

The sleep-wakefulness was visually scored in 10 sec epochs as wakefulness, which included both active and quiet waking, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Wakefulness was identified by the simultaneous presence of desynchronized EEG with high (active W) or reduced (quiet W) EMG activity, whereas NREM sleep was identified by the simultaneous presence of synchronized EEG without transient periods of desynchronization along with reduced EMG activity. REM sleep was identified by the concomitant presence of desynchronized EEG with no muscle tone (Thakkar et al., 2003). Sleep-wakefulness data was grouped separately for light and dark period. We also examined the effects of acute one day binge alcohol consumption on bouts and duration of each state.

Measurement of BAC

Blood withdrawal requires handling, restraint and may cause pain. This may affect sleep and may confound our results. Thus, a separate group of rats was used for BAC measurement. These animals did not undergo any surgery or sleep recording. However, these animals were exposed to the same binge alcohol administration protocol as described above. BAC was measured at light and dark onset on post-binge Day 1 and at light onset on post-binge Day 2. BAC was measured as described previously (Thakkar et al., 2010b). Briefly, the rat was removed from its home cage, gently swaddled in a towel and a sample of blood (~5 μ L) was collected using tail-snip method. The collected blood sample was centrifuged to separate plasma and stored at -20°C until analyzed. BAC was analyzed using the Ethanol Assay Kit (Biomedical Research Service, (Buffalo, NY).

Statistical analysis

One-way Repeated Measures (RM) ANOVA (Prism; Graphpad Software, La Jolla, CA) followed by Dunnet's post-hoc test was used to examine the effects of acute binge alcohol administration on sleep-wakefulness with $\alpha = 0.05$.

RESULTS

Alcohol Dose—The total dose of alcohol administered to rats ($N = 7$; Mean $\pm$ SEM = 14.6 ± 0.20 g/Kg) subjected to sleep recording was comparable to the total dose of alcohol administered to rats ($N = 4$) used for BAC measurement (Mean $\pm$ SEM = 14.3 ± 0.19 g/Kg).

BAC—At light onset on post-binge Day 1, Mean ($\pm$ SEM) BAC was 212 ± 40 mg/dL suggesting that the animals were exposed to binge pattern of drinking. At dark onset on post-binge Day 1, mean ($\pm$ SEM) BAC was reduced to 54 ± 15 mg/dL. At light onset on

post-binge Day 2, BAC was zero suggesting that alcohol was completely eliminated from the system by light onset on post-binge Day 2.

Light (sleep) Period

Sleep-Wakefulness—RM ANOVA revealed a significant main effect of binge alcohol treatment on wakefulness ($F_{3, 27} = 6.9$; $p = 0.003$) and NREM sleep ($F_{3, 27} = 10.0$; $p = 0.0004$). REM sleep was unaffected ($F_{3, 27} = 1.7$; $p = 0.2$) (Figure 1A).

Interestingly, on post-binge Day 1, while the amount of time spent in wakefulness (~19%) and REM sleep (~35%) was reduced, the amount of time spent in NREM sleep (~13%) was increased. However, none of the values achieved significance as revealed by post-hoc (Dunnett's) test (Figure 1A).

In contrast to post-binge Day 1, binge alcohol administration had significant effects on sleep-wakefulness on post-binge Day 2 after alcohol was completely eliminated (BAC = 0). As compared to baseline, the amount of time spent in wakefulness (Mean $\pm$ SEM; baseline = 28.5 ± 1.5 ; post-binge Day 2 = 40.9 ± 4.3) was significantly ($p < 0.05$; Dunnett's test) increased (>40%), whereas the amount of time spent in NREM (Mean $\pm$ SEM; baseline = 63.8 ± 1.2 ; post-binge Day 2 = 52.6 ± 3.5) sleep was significantly ($p < 0.05$; Dunnett's test) reduced (~17%). REM sleep remained unaffected (Figure 1A). Increased wakefulness with a concomitant reduction in NREM sleep during normal sleep (light) period of rodents is suggestive of insomnia (Brower et al., 2001; Thakkar et al., 2010a).

On post-binge Day 3, the amount of time spent in sleep-wakefulness was comparable to baseline suggesting that sleep-wakefulness changes observed on post-binge Day 2 were normalized on post-binge Day 3 (Figure 1A).

Bouts and Duration—To further understand the underlying contributor toward binge alcohol induced changes in sleep-wakefulness, we examined bouts and duration of each behavioral state on post-binge Days 1 and 2.

As described in Figure 1B, binge alcohol administration had a significant main effect on bouts of wakefulness ($F_{2, 20} = 6.5$; $p = 0.01$) and NREM sleep ($F_{2, 20} = 8.5$; $p = 0.005$). REM sleep was unaffected ($F_{2, 20} = 2.2$; $p = 0.2$). In contrast, only NREM sleep duration was affected ($F_{2, 20} = 15.1$; $p = 0.0005$; Figure 1C).

Post-hoc analysis revealed there was no change in bouts and duration on post-binge Day 1. However, on post-binge Day 2, there was a significant ($p < 0.05$) increase in number of wakefulness (Mean $\pm$ SEM; baseline = 150.3 ± 35 ; post-binge Day 2 = 238 ± 21.4) and NREM sleep bouts (Mean $\pm$ SEM; baseline = 158.1 ± 32.8 ; post-binge Day 2 = 242.7 ± 21.9 ; Figure 1B) coupled with a significant ($p < 0.01$) reduction in NREM sleep epoch duration (Mean $\pm$ SEM; baseline = 215.2 ± 33.6 ; post-binge Day 2 = 97.7 ± 10.5 ; Figure 1C). These results suggest that animals exposed to binge alcohol treatment had no problems initiating NREM sleep, however they were unable to maintain NREM sleep resulting in insomnia-like symptoms during light period on post-binge Day 2 (see Figure 1A).

Dark (active) Period

Sleep-Wakefulness—In contrast to the light period, RM ANOVA revealed a significant main effect of binge alcohol treatment only on NREM sleep ($F_{3, 27} = 3.2$; $p = 0.05$). Wakefulness ($F_{3, 27} = 2.07$; $p = 0.14$) and REM sleep ($F_{3, 27} = 0.7$; $p = 0.6$; Figure 2A) was unaffected.

There was no change in sleep-wakefulness on post-binge Day 1. However, on post-binge Day 2, as compared to baseline (Mean $\pm$ SEM = 23.5 ± 1.9), the amount of time spent in NREM sleep (Mean $\pm$ SEM; post-binge Day 2 = 34.8 ± 3.1) was significantly ($p < 0.05$) increased (Figure 2A). Increased NREM sleep during normal active (dark) period of rodents is suggestive of excessive daytime sleepiness. The amount of time spent in sleep-wakefulness returned to baseline values on post-binge Day 3 (Figure 2A).

Bouts and Duration—As described in Figure 2B, binge alcohol administration had a significant main effect on bouts of wakefulness ($F_{2, 20} = 6.9$; $p = 0.01$) and NREM sleep ($F_{2, 20} = 6.2$; $p = 0.01$). REM sleep remained unchanged ($F_{2, 20} = 1.2$; $p = 0.3$). Only the duration of wakefulness was affected during the dark period ($F_{2, 20} = 5.8$; $p = 0.02$; Figure 2C).

Post-hoc analysis revealed that during the dark period on post-binge Day 2, binge alcohol treatment significantly ($p < 0.01$) reduced wakefulness epoch duration (Mean $\pm$ SEM; baseline = 352.9 ± 55.0 ; post-binge Day 2 = 165.2 ± 20.3 ; Figure 2C) coupled with a significant ($p < 0.01$) increase in wakefulness bouts (Mean $\pm$ SEM; baseline = 85.9 ± 8.2 ; post-binge Day 2 = 147.3 ± 12.8 ; Figure 2B). These results suggest that during the dark period on post-binge day 2, the animals were unable to maintain their wakefulness.

In contrast to wakefulness, only NREM sleep bouts were significantly ($p < 0.01$) increased (Mean $\pm$ SEM; baseline = 83.3 ± 6.5 ; post-binge Day 2 = 147.4 ± 15.8 ; Figure 2B). NREM sleep duration remained unchanged.

DISCUSSION

The results of our study suggest that acute binge alcohol exposure to rats reversed sleep-wakefulness with the animals displaying insomnia-like symptoms (increased wakefulness; reduced NREM sleep) during their normal sleep (light) period and excessive “daytime” sleep (increased NREM sleep) during their normal active or dark period. The reversal of sleep-wakefulness occurred only after alcohol was completely eliminated from the system (BAC = 0) suggesting that sleep disruptions accompany “hangover/withdrawal” that is observed following binge (heavy) alcohol consumption. This is the first study documenting the effects of acute binge alcohol administration on sleep-wakefulness and demonstrating that alcohol hangover accompanies reversal of sleep-wakefulness.

Our experimental design was simple and straightforward. We used “within subject” design because it offers several advantages including increased statistical power without increasing animal numbers and a reduction in error variance associated with individual differences. Animal studies suggest that to mimic “binge” effects multiple exposures to alcohol are

necessary (Courtney and Polich, 2009). A shortened version (one day) of the Majchrowicz's protocol was used to mimic human binge alcohol consumption (Majchrowicz, 1975). This easy to use method has been extensively used [>300 papers citation of the original article in last 20 years (Faingold, 2008)] as a model to understand the effects of binge alcohol administration in experimental animals (Crews and Nixon, 2009; Crews et al., 2004) and resembles the route of alcohol intake in humans, the degree of alcohol intoxication achieved during binge-drinking episodes, and results in BAC in the range of those reported in trauma patients in emergency rooms across the United States (Greiffenstein et al., 2007; Courtney and Polich, 2009; Sprow and Thiele, 2012)] The animals used for BAC measurements were subjected to identical binge alcohol administration protocol and administered comparable amounts of alcohol.

One major findings of our study was that minimal sleep-wakefulness changes occurred on post-binge Day 1 especially during the light period, when BAC was relatively high (>200 mg/dL). Although the animals spent more time in NREM sleep, the values did not achieve significance.

Interestingly major sleep-wakefulness changes were observed on post-binge Day 2 after BAC was zero suggesting that "hangover" observed following heavy (binge) alcohol administration is accompanied by severe sleep disruptions including insomnia and excessive daytime sleepiness.

Alcohol hangover, defined by the presence of several unpleasant/aversive symptoms that are observed when BAC is zero, is the most common negative consequence of binge alcohol consumption (Verster et al., 2010; Penning et al., 2010). While alcohol hangover research is in its infancy, evidence exists to suggest that individuals experiencing hangover may consume (self-medicate) more alcohol to alleviate the symptoms of alcohol hangover resulting in the initiation of vicious cycle that may eventually culminate into the development of alcohol use disorder (Piasecki et al., 2010; Ehlers et al., 2013). In fact, heavy alcohol consumption, hangover resistance, and hangover frequency may each indicate low alcohol sensitivity which is an established risk factor for the development of alcohol dependence (Piasecki et al., 2012). Are sleep disruptions observed during alcohol hangover causal or consequence to alcohol hangover? This is yet an unanswered question. However, alcohol is amongst the most commonly used sleep aid to "self-medicate" sleep problems (Brower et al., 2001; Roehrs and Roth, 2001b), it is very likely that an individual consume more alcohol during alcohol hangover may be to self-medicate/treat sleep disruptions.

The results of our study suggests that impaired NREM maintenance was the cause for insomnia-like symptoms observed during normal sleep (light) period on post-binge Day 2. Thus, the animals were attempting to and initiating NREM sleep, but unable to maintain it resulting in increased NREM to wake transitions and increased wakefulness bouts. Although the underlying neuronal mechanism responsible for dysfunctional NREM maintenance is unknown and under-investigation, based on our previous studies (Sharma et al., 2010; Sharma et al., 2013b; Thakkar et al., 2010b), insomnia-like symptoms observed post-binge may be due to hyper-activation of wakefulness-promoting systems (Sharma et al., 2010).

In contrast, reduction in wakefulness maintenance coupled with increased NREM bouts appeared to be the underlying cause of increased NREM sleep (excessive daytime sleepiness) observed during the normal active (dark) period of the animals. Since alcohol treated rats were awake in the light period, increased homeostatic drive may be the likely cause for impaired wake maintenance in the following dark (active) period. However, increased homeostatic drive may not be sufficient to override the circadian alerting signal during their normal active period. Thus, as evident from increased wakefulness bouts, rats were attempting to initiate wakefulness but unable to maintain it.

To conclude, our study is the first to demonstrate that rats exposed to acute binge (heavy) alcohol displayed severe sleep disruptions including insomnia during normal sleep period and excessive sleep during normal active period. This reversal of sleep-wakefulness was observed during alcohol “hangover”, after alcohol was completely eliminated from the system and BAC was zero.

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Figure 1. Effects of acute binge alcohol administration on sleep-wakefulness during the light period

A) There was a significant increase in the amount of time spent in the wakefulness with a concomitant reduction in the amount of time spent in NREM sleep on post-binge Day 2. REM sleep remained unaffected. There was no change in sleep-wakefulness on post-binge Day 1 and the changes in sleep-wakefulness observed on post-binge Day 2 were normalized on post-binge Day 3.

B) Acute binge alcohol administration significantly increased bouts of wakefulness and NREM sleep on post-binge Day 2. REM bouts were unaffected.

C) Only NREM duration was significantly reduced on post-binge Day 2. Wakefulness and REM duration remained unchanged. * = $p < 0.05$; ** = $p < 0.01$. See text for details.

Figure 2. Effects of acute binge alcohol administration on sleep-wakefulness during the dark period

A) Significant increase in the amount of time spent in NREM sleep was observed during the dark period on post-binge Day 2. Wakefulness and REM sleep did not show any change.

(B) Acute binge alcohol caused a significant increase in wakefulness and NREM bouts on post-binge Day 2. REM bouts were unaffected.

(C) Only wakefulness duration was significantly reduced during the dark period on post-binge Day 2. NREM and REM duration remained unaffected. * = $p < 0.05$; ** = $p < 0.01$. See text for details.

Table 1

Level of intoxication and dose of alcohol

Signs of intoxication	Dose of alcohol (g/Kg)
Neutrality	5.0
Sedation- reduced muscle tone and general sleepiness	4.0
Mild ataxia- sluggish movement and loss of coordination	4.0
Severe ataxia- pelvis and abdomen remain on the ground	3.0
Loss of righting reflex	No alcohol
Coma	No alcohol