

Article

Hyperalgesia after a Drinking Episode in Young Adult Binge Drinkers: A Cross-Sectional Study

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Abstract

Aims: Rodent studies propose potential mechanisms linking excessive drinking and pain hypersensitivity (hyperalgesia), such that stress hormones (i.e. epinephrine and cortisol) mediate induction and maintenance of alcohol withdrawal-induced hyperalgesia. The first aim of this study was to examine whether hyperalgesia would occur within 48 h after a drinking episode in healthy young adult binge drinkers. The second was to examine whether stress hormones and negative effect would be associated with binge drinking or alcohol withdrawal-associated hyperalgesia.

Methods: A cross-sectional experiment was conducted in five groups with naturally occurring drinking (mean age = 19.6, range 18–29 years): abstainers ($n = 43$, 54% female), moderate drinkers with ($n = 50$, 50% female) or without recent drinking (i.e. within 48 h, $n = 23$, 26% female) and binge drinkers with ($n = 36$, 58% female) or without recent drinking ($n = 25$, 44% female). All types of drinkers endorsed drinking about 2–3 times a month and 2–3 years of drinking history.

Results: Muscle pressure pain thresholds were significantly lower in the binge group with recent drinking compared to other groups, but cutaneous mechanical and heat pain thresholds were not significantly different across the five groups. Basal epinephrine levels were significantly higher in binge groups regardless of recent drinking, but cortisol and negative effect were not significantly different across the five groups.

Conclusions: This is the first study to show that alcohol withdrawal-associated muscle hyperalgesia may occur in healthy episodic binge drinkers with only 2–3 years of drinking history, and epinephrine may play a role in binge drinking-associated hyperalgesia.

INTRODUCTION

Up to 35% of young adults report binge drinking, a significant health risk behavior (Substance Abuse and Mental Health Services Administration, 2019). Binge drinking is defined as consuming at least 4(women)/5(men) standard drinks within 2 h (National Institute on Alcohol Abuse and Alcoholism, 2004), which increases blood alcohol concentrations (BAC) to 0.08 g% and often causes blackouts (Hingson *et al.*, 2016) and neurotoxicity (Alfonso-Loeches *et al.*, 2013). Following binge drinking, unpleasant physical, neurocognitive and psychological symptoms develop and persist several hours after

BAC returns to 0 g% (Swift and Davidson, 1998). These alcohol withdrawal symptoms, commonly called hangover symptoms in the context of young adults' binge drinking, disappear within 2 days (Sellers, 1988).

Rodent studies show that pain hypersensitivity (hyperalgesia) occurs during alcohol withdrawal. This hyperalgesia during withdrawal may explain the relationship between excessive drinking and pain. Reviews, largely based on rodent research, highlight the disrupted stress system as a possible mechanism linking alcohol to pain (Egli *et al.*, 2012; Edwards *et al.*, 2020;

Robins *et al.*, 2019). Repeated exposure to alcohol intoxication and withdrawal episodes enhances stress signaling and leads to hyperalgesia. Rats show analgesic responses after an ethanol diet, followed by hyperalgesic responses during alcohol withdrawal (Gatch and Lal, 1999). A study also shows that rats develop hyperalgesia to muscle pressure pain during withdrawal after 1 cycle of an ethanol binge diet, and this hyperalgesia worsens with repeated binges up to 4 cycles (Dina *et al.*, 2006). Surprisingly, rats on a continuous ethanol diet do not develop hyperalgesia, highlighting the role of 'withdrawal', not excessive drinking, in the development of hyperalgesia. Rodent studies have also identified several mechanisms driving the development of alcohol withdrawal-induced hyperalgesia, including increased circulating levels of stress hormones (epinephrine and glucocorticoids, Dina *et al.*, 2008). Blocking the secretion and action of epinephrine or cortisol reverses already occurring hyperalgesia and prevents the occurrence of withdrawal-induced hyperalgesia despite continued cycles of binge and withdrawal (Dina *et al.*, 2008).

Alcohol withdrawal-induced hyperalgesia has received limited attention in the human literature. One human study demonstrated evidence of alcohol withdrawal-associated hyperalgesia in which middle-aged men with alcohol dependence without neuropathy showed reversible pain hypersensitivity during alcohol detoxification (Jochum *et al.*, 2010). This study demonstrated that withdrawal-associated hyperalgesia occurs before the development of alcoholic neuropathic pain. However, it is unknown whether withdrawal-associated hyperalgesia would occur even before the development of alcohol dependence such as in episodic binge drinkers and whether stress hormones are similarly implicated in alcohol withdrawal-associated hyperalgesia of humans. If so, lowering stress hormones by psychological and pharmacological intervention might provide a preventative approach for binge drinkers who are at risk for transitioning from episodic binge drinking to alcohol dependence (e.g. family history of alcoholism, childhood adversity, Fenton *et al.*, 2013) and alcoholic neuropathic pain (e.g. female, Ammendola *et al.*, 2000). Without these preventive approaches, recurrent alcohol intoxication and withdrawal episodes may lead to dysregulation of brain reward and stress systems during the development of alcohol dependence (Egli *et al.*, 2012). Over time, negative effect and persistent pain may play key roles in continued drinking because alcohol provides immediate relief from them, which persist and worsen during alcohol withdrawal (Egli *et al.*, 2012). Eventually, in advanced stages of drinking, irreversible and painful alcoholic neuropathy may develop.

The primary aim of this study was to investigate whether alcohol withdrawal-associated hyperalgesia would occur in healthy young adult binge drinkers. Second, we examined whether measures of psychological and physiological stress would be elevated in binge drinkers who drank alcohol within 2 days. To achieve these aims, we conducted a cross-sectional study to evaluate pain sensitivity after naturally occurring alcohol use. We hypothesized that binge drinkers who drank alcohol within 2 days would show (a) pain hypersensitivity and (b) elevated psychological (negative effect) and physiological (stress hormones) stress levels compared to binge drinkers who did not drink within 2 days, moderate drinkers and abstainers.

METHODS

Recruitment

The Texas A&M University Institutional Review Board approved the study procedures, which were conducted in accordance with the

Helsinki Declaration. All participants provided informed consent. Inclusion criteria were healthy adults between 18 and 30 years of age. Exclusion criteria were (a) any chronic physical and mental health issues, (b) prescription medication use (except contraceptives and vitamins), (c) needle phobia and (d) an injury or skin condition on the feet (pain testing site).

Potential participants completed an online prescreening survey evaluating health status and drinking history. They were asked to select one that describes their drinking pattern, with options never, former and current drinker. Those who endorsed 'Never' (57%) were classified as abstainers. 'Current' drinkers (37%) were asked to complete the Daily Drinking Questionnaires (DDQ, Collins *et al.*, 1985). On the DDQ, participants reported the number of standard drinks and hours spent drinking for a typical week in the last 30 days. Moderate drinking was defined as consuming <4 (women)/5 (men) standard drinks on any occasion.

Of the total 2226 people who completed the prescreening (12% current binge drinkers), 177 people participated in this study. Before the laboratory visit, participants were instructed to avoid any pain and allergy medicine 3 days before the experiment and avoid caffeine and vigorous exercise 4 h before the experiment. After quantitative sensory testing (QST), participants reported their last drinking on the exit survey. Most participants (85%) received class credit for their participation, while the rest received the opportunity to win one of three \$100 gift cards in a raffle.

Questionnaires

The following self-report measures assessed binge drinkers' baseline psychological characteristics and emotional responses to pain testing. The Depression Anxiety Stress Scales (DASS) assessed the severity of depression, anxiety and life stress symptoms over the past week (Antony *et al.*, 1998). Total scores range from 0 to 42 for each symptom domain, with normal ranges <10 for depressive, <8 for anxiety and <15 for stress symptoms (Lovibond and Lovibond, 1995). The Hangover Symptoms Scale (HSS) was administered to assess the frequency of 13 hangover symptoms over the past 12 months (Slutske *et al.*, 2003), with scores ranging from 0 (0% of the time) to 4 (100% of the time). Items were dichotomized to identify symptom presence (1 = 1–4) or absence (0 = 0) and then summed. Therefore, total scores range from 0 to 13, with higher scores indicating more hangover symptoms. The Acute Hangover Scale (AHS) was used to assess nine acute hangover symptoms (i.e. hangover, thirsty, tired, headache, dizziness, loss of appetite, stomachache, nausea and heart racing) rated on a 0: None to 7: Incapacitating scale (Rohsenow *et al.*, 2007). The Spielberger State-Trait Anxiety Inventory-6 (STAI) evaluated emotional responses to pain testing, with total scores ranging from 6 to 24 and higher scores indicating higher anxiety (Marteau and Bekker, 1992).

Quantitative Sensory Testing. Because alcoholic polyneuropathy often affects lower extremities (Chopra and Tiwari, 2012), pain testing was conducted on the dorsum of the nondominant foot (L5 dermatome). The QST protocol of the German Research Network was used to measure cutaneous mechanical, heat and muscle pressure pain thresholds (PPTs) (Rolke *et al.*, 2006). Briefly, the cutaneous mechanical pain threshold (MPT) was measured by applying von Frey filaments (0.6, 1.4, 4, 6, 15, 26 and 60 gF, Stoelting Co. USA) in an ascending, and then a descending order. To prevent sensory fatigue and local sensitization, each threshold test occurred at a different location with an intertrial interval \geq 10s. Individual MPT

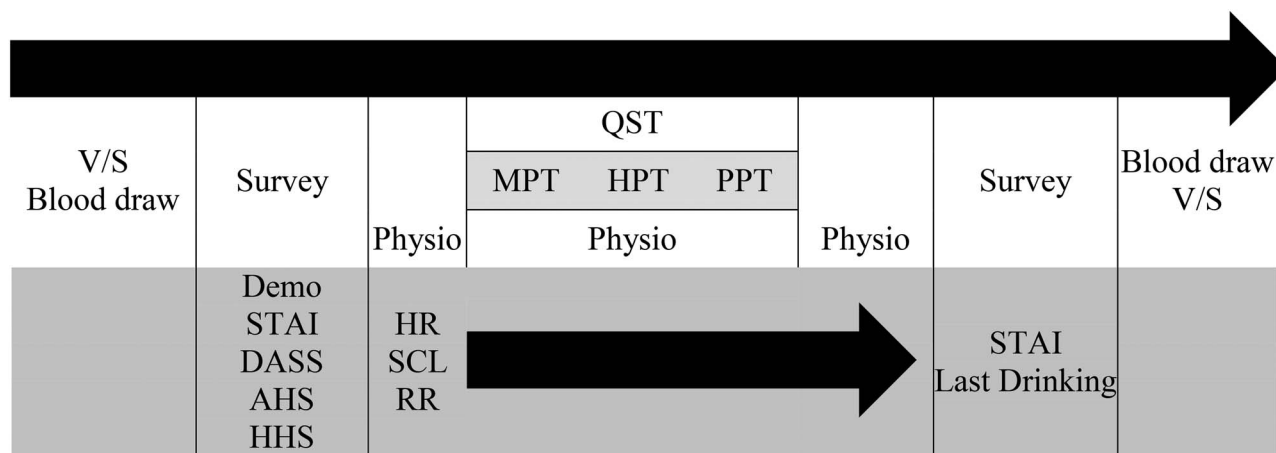


Fig. 1. Experiment timeline [1 h]. V/S: Vital Sign including Blood Pressure, HR, and BT. MPT: Cutaneous Mechanical Pain Threshold, HPT: Heat Pain Threshold, PPT: Muscle Pressure Pain Threshold. Demo: Demographics, STAI: State-Trait Anxiety Inventory-6; DASS (Depression Anxiety Stress Scales); AHS: Acute Hangover Scale; HSS: Hangover Symptom Scale; HR: Heart Rate; BT: Body Temperature; SCL: Skin Conductance Level; RR: Respiration Rate.

was calculated as the geometric mean of the three series of ascending and descending stimulus intensity ratings. If participants reported no painful sensation to the highest force von Frey (60 gF), the next highest force (100 gF) in the series was used as their pain threshold (Cameron *et al.*, 2008). Heat pain threshold (HPT) was measured using a 9-cm² Peltier thermode (ATS, Medoc Ltd., Israel). Temperature was ramped at 1 °C/s (baseline temperature 32°C) until participants indicated their first pain sensation. Tests were repeated three times at 30 s intervals and the values were averaged to calculate individual HPT. Muscle PPT was measured three times using a handheld algometer (FPX 50 model, Wagner Instrument, USA) at 30 s intervals and the values averaged to calculate individual PPT.

Blood collection. Blood was collected in a chilled EDTA tube before and after QST. The blood samples were centrifuged for 15 min at 1000 × g in a cold room (4°C), aliquoted into 0.5-ml tubes, and stored in a –80°C freezer until assayed.

Enzyme-linked immunosorbent assay. Duplicate samples were analyzed according to the manufacturer's manual. Abnova (No KA1877) and IBL international (RE52061) kits were used for Epinephrine and Cortisol, respectively.

Physiological measures. Continuous heart rate (HR), skin conductance level (SCL) and respiration rate (RR) were sampled at 1000 Hz using a MP150 (BIOPAC Systems, USA), interfaced with AcqKnowledge 4.2 for data acquisition. LabVIEW 8.0 was also used to generate a digital signal from the National Instrument 6008USB device connected to a BIOPAC Systems STP100C and UIM100C. A finite impulse response (FIR) bandpass filter was used to remove movement artifacts from HR (0.5 and 35 Hz) (Ruha *et al.*, 1997) and RR (0.05 and 1.0 Hz). To remove artifacts from SCL, a 1 Hz FIR lowpass filter was used. After filtering, all data were visually inspected. Filtering corrected most noise in RR and SCL. However, HR data from three subjects containing uncorrectable noises (e.g. extreme movement artifacts) were not analyzed.

Procedures

To recruit participants who voluntarily consumed alcohol, the experiment was conducted between Thursday and Sunday. For ethical reasons, participants did not receive any instructions about alcohol consumption. Participants who chose to consume alcohol within 2 days were classified in 'recent' alcohol drinking groups. Additionally, the experiment time was between 12 pm and 6 pm to minimize the effect of diurnal variation on pain and stress hormones. Participants were blinded to the study hypotheses and the experimenter conducting QSTs was blinded to participants' drinking patterns.

Figure 1 depicts the experiment timeline. Before and after the blood draw, BP, HR and body temperature were measured to make sure the levels were within normal limits. In the testing room, baseline physiological data were collected 5 min after the survey. The interval between different QSTs was 5 min.

Statistical analysis

To examine the first hypothesis, a multivariate analysis of variance (MANOVA) with three pain thresholds was followed by a least significant difference (LSD) test. For the second hypothesis, a repeated-measures analysis of variance (ANOVA) compared the group difference in stress hormones and effective responses to QST. Then, an analysis of covariance (ANCOVA) examined how much of the group difference in pain sensitivity would be accounted for by stress hormones and negative effect. All statistical tests were two-tailed and *P* values < 0.05 were considered significant. SPSS 22 was used for all analyses.

Sample size calculation. This study was designed to recruit five naturally occurring groups: (a) abstainers, (b) moderate drinkers with a recent drinking episode, (c) moderate drinkers without a recent drinking episode, (d) binge drinkers with a recent drinking episode (main group of interest) and (e) binge drinkers without a recent drinking episode. Large effects of alcohol withdrawal on pain threshold were reported (Cohen's *d* > 1.65, Dina *et al.*, 2006, Dina *et al.*, 2008; Jochum *et al.*, 2010). Sample size calculation indicated that at least 25 participants were needed in each group to achieve 95% power and an α of 0.05 for a between-subjects design. Our main interest was to evaluate group differences by drinking patterns

Table 1. Demographics and drinking patterns

	Abstainers	Moderate drinkers		Binge drinkers		χ^2 or F	P
		No recent drinking	Recent drinking	No recent drinking	Recent drinking		
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)		
N	43	50	23	36	25		
(Male/Female)	(20/23)	(25/25)	(17/6)	(15/21)	(14/11)	6.69	0.153
% Caucasian	60.5	64.0	73.9	63.9	80.0	3.57	0.467
% Cigarette use	2.3	6.0	13.0	13.9	8.0	9.87	0.043
Age	18.7(1.2) ^a	20.1(2.5) ^b	20.3(2.0) ^b	19.8(1.8) ^b	19.6(2.3) ^{ab}	4.35	0.002
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	F	P
Ages at first drink	–	18.0(1.9) ^a	16.8(1.9) ^b	17.1(1.3) ^b	16.5(1.0) ^b	4.87	0.003
Years of drink	–	2.2(2.1)	2.8(1.9)	2.6(1.9)	3.0(2.3)	0.89	0.448
Frequency	–	2.0(1.4)	2.0(1.6)	2.6(1.5)	2.2(2.4)	0.82	0.488
HSS	–	3.0(2.8) ^a	4.0(3.0) ^a	5.1(3.0) ^b	6.6(2.9) ^c	10.22	<0.001
AHS	–	5.6(3.7) ^a	5.6(3.0) ^a	6.3(4.0) ^a	10.2(9.3) ^b	4.94	0.003

Recent drinking: Alcohol consumption within 48 h before the experiment; χ^2 statistics were used for gender, ethnicity and cigarette use; superscripts of *a*, *b* and *c* indicate significant difference in post-hoc analysis. HSS: Hangover Symptom Scale; AHS: Acute Hangover Scale.

and we sought to recruit an equal number of men and women per group. Thus, all the data were analyzed and presented by drinking group, but gender and gender by group interactions were examined and significant results were noted, if any.

Missing data. There were few missing values (~1.7%), which were replaced with overall means. For pain data, three participants did not undergo HPT tests because of equipment malfunctioning. Therefore, these three participants' physiological data were replaced with the overall means. For psychological state variables, one binge drinker did not complete the STAI at baseline.

Participants

Table 1 depicts the demographics. There were no group differences in gender, race/ethnicity or cigarette use (P s > 0.097). The abstainer group was about 1 year younger than the other groups, but all were young adults.

The age of first alcohol use was somewhat older in the moderate drinkers than the others, but no difference was found in years of regular alcohol use ($P = 0.448$). An ANOVA indicated no group difference in drinking frequency endorsed on the DDQ ($P = 0.488$); all types of drinkers endorsed drinking about 2–3 times a month. The respective means of typical drinks were 2.5 ($SD = 1.6$) and 3.1 drinks ($SD = 2.4$) for female and male moderate drinkers, and 6.6 ($SD = 3.2$) and 10.3 ($SD = 10.2$) for female and male binge drinkers. On the HSS, binge drinkers reported more hangover symptoms for the past 12 months. Notably, the HSS scores were even higher in the binge drinkers with recent drinking than those without it. Additionally, more hangover symptoms were reported on the AHS by binge drinkers with recent drinking, being consistent with the self-reported recent drinking episode. The respective means of recent drinks were 1.8 ($SD = 1.0$) and 2.0 ($SD = 1.5$) for female and male moderate drinkers, and 5.0 ($SD = 1.6$) and 6.0 ($SD = 4.9$) for female and male binge drinkers.

Baseline psychological and physiological characteristics

Baseline psychological characteristics were similar between the groups (Kruskal–Wallis tests' P s > 0.136) except for depressive symptoms ($P = 0.022$). Post-hoc comparisons with the Mann–Whitney test indicated that moderate and binge drinker groups reported more depressive symptoms than the abstainer group (Table 2). Depressive symptoms did not differ between abstainers and moderate drinkers with recent drinking ($P = 0.075$).

In comparing the baseline physiological states, a one-way ANOVA indicated difference only in SCLs, $F(4, 283) = 3.12$, $P = 0.017$. LSD post-hoc analysis indicated that higher SCLs were observed in the two moderate drinker groups and the binge drinker group with recent drinking, P s < 0.05 (Table 2).

RESULTS

Pain sensitivity

To examine group differences in cutaneous mechanical, heat and muscle PPTs, a MANOVA was conducted. The results revealed a significant main effect of group, Wilk's $\Lambda = 0.80$, $P < 0.001$. Follow-up univariate analysis indicated that only muscle PPT was different between the groups, $F(4, 165) = 7.10$, $P < 0.001$, partial $\eta^2 = 0.14$. LSD post-hoc analysis indicated that the binge group without recent drinking, $\ln M = 1.02$, $\ln SD = 0.50$, showed lower muscle PPTs when compared to the moderate drinking group without recent drinking, $\ln M = 1.27$, $\ln SD = 0.47$, $P = 0.013$ (Fig. 2). These results indicate the divergent effects of alcohol consumption on muscle PPT. Specifically, moderate drinking was associated with an increase in PPT, whereas binge drinking was associated with a decrease in PPT. Notably, the binge group with recent drinking, $\ln M = 0.67$, $\ln SD = 0.51$, showed reduced PPT compared to all the other groups, P s < 0.005. Lastly, neither cutaneous MPT ($P = 0.148$) nor heat pain threshold ($P = 0.393$) differed significantly between groups, suggesting that binge drinking and alcohol withdrawal were unrelated to cutaneous mechanical and heat pain thresholds in young adult binge drinkers.

Table 2. Experiment 1 baseline psychological and physiological characteristics

	Abstainers		Moderate drinkers				Binge drinkers			
			No recent drinking		Recent drinking		No recent drinking		Recent drinking	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Psychological variables										
DASS-DEP	3.8 ^a	5.2	6.2 ^b	7.2	5.9 ^{ab}	6.5	5.3 ^b	5.1	7.9 ^b	7.3
DASS-ANX	4.1	4.5	4.8	5.0	3.7	3.7	4.6	5.1	6.3	4.5
DASS-STR	8.9	6.0	8.9	6.3	8.6	6.6	9.3	6.6	11.0	6.7
Psychological states										
STAI	9.2	2.3	9.2	2.3	9.4	2.5	9.4	3.1	9.4	2.6
Physiological states										
HR (beat/min)	72.7	8.9	75.6	10.7	72.0	9.5	74.3	10.1	72.8	9.5
SCL (sqrtμS)	2.0 ^a	0.7	2.5 ^b	0.8	2.5 ^b	0.6	2.1 ^{ab}	0.6	2.4 ^b	0.8
RR (breath/min)	13.6	3.9	14.2	2.8	14.1	3.3	13.2	3.2	13.9	3.0
SBP (mmHg)*	112.0	10.0	114.5	13.1	119.4	13.7	113.9	12.7	116.8	12.9
DBP (mmHg)*	70.6	5.7	71.8	7.4	72.7	10.2	72.1	9.0	71.0	6.5

The means with the different superscript letter are significantly different at *P* value of 0.05. DASS (Depression Anxiety Stress Scales)-DEP: Depression, ANX: Anxiety, STR: Stress; STAI: State-Trait Anxiety Inventory-6; HR: Heart Rate, SCL: Skin Conductance Level, RR: Respiration Rate; SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

*Kruskal-Wallis followed by Mann-Whitney *U* test.

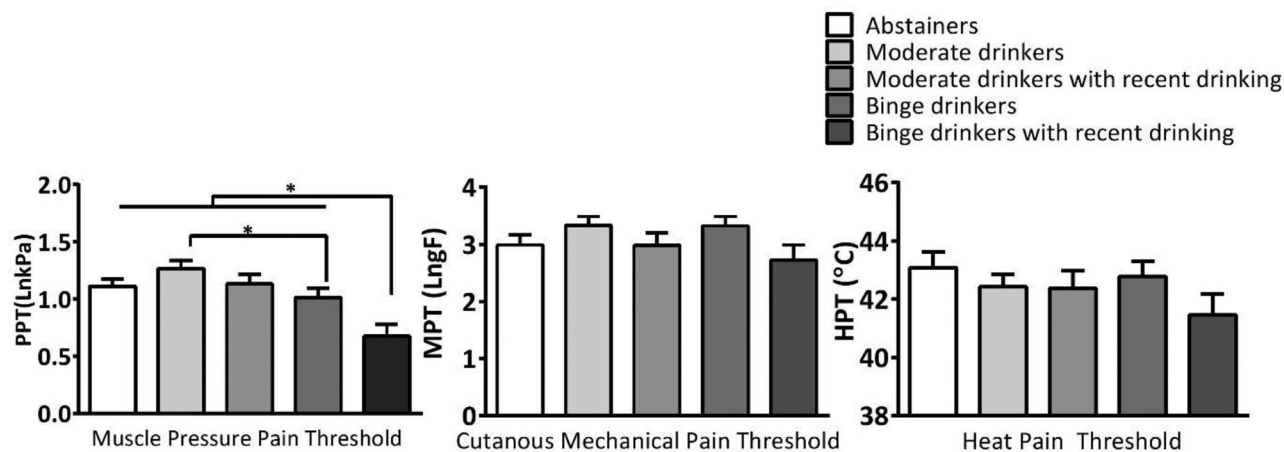


Fig. 2. Comparison of muscle pressure pain, cutaneous mechanical and heat pain thresholds between the groups with different drinking patterns (Error bars = SEM).

Stress hormones in relation to drinking patterns and pain sensitivity

A time \times gender \times group repeated measures ANOVA was conducted for epinephrine (Fig. 3, Upper Left). The results showed no significant time ($P = 0.296$) nor interaction effects ($P_s > 0.245$, Fig. 3, upper right). There were significant main effects of group, $F(4, 167) = 2.66$, $P = 0.035$, and gender, $F(1, 167) = 10.62$, $P = 0.001$, but no significant gender \times group interaction ($P = 0.834$). The main effect of gender on basal epinephrine was driven by higher levels in men, $\sqrt{M} = 14.91$, $\sqrt{SD} = 6.15$, compared to women, $\sqrt{M} = 11.78$, $\sqrt{SD} = 6.58$.

An LSD post-hoc analysis showed that binge drinkers without recent drinking, $\sqrt{M} = 15.43$, $\sqrt{SD} = 5.99$, showed elevated epinephrine levels compared to abstainers, $\sqrt{M} = 11.56$, $\sqrt{SD} = 5.67$, and moderate drinkers without recent drinking, $\sqrt{M} = 12.34$, $\sqrt{SD} = 5.95$. Different from expectation, no significant difference

was found between the binge group with and without recent drinking ($P = 0.562$). These results suggest that binge drinking, but not alcohol withdrawal, was associated with an increase in basal epinephrine levels. A subsequent ANCOVA controlling for basal epinephrine levels indicated that the group difference in muscle PPT remained significant, $F(4, 171) = 6.21$, $P < 0.001$, but the effect size was reduced by 7%, partial $\eta^2 = 0.13$, suggesting basal epinephrine levels explained a small portion of the variance in binge drinking-associated hyperalgesia.

Next, a time \times gender \times group repeated measures ANOVA was conducted on cortisol. The results showed a significant effect of time, $F(4, 167) = 127.85$, $P < 0.001$, but no other significant main or interaction effects ($p_s > 0.138$). Cortisol levels decreased after the QSTs ($M = -26.8$, $SD = 30.5$, Fig. 3, Lower right). The lack of a group difference in cortisol suggests cortisol was unrelated to the group difference in PPT.

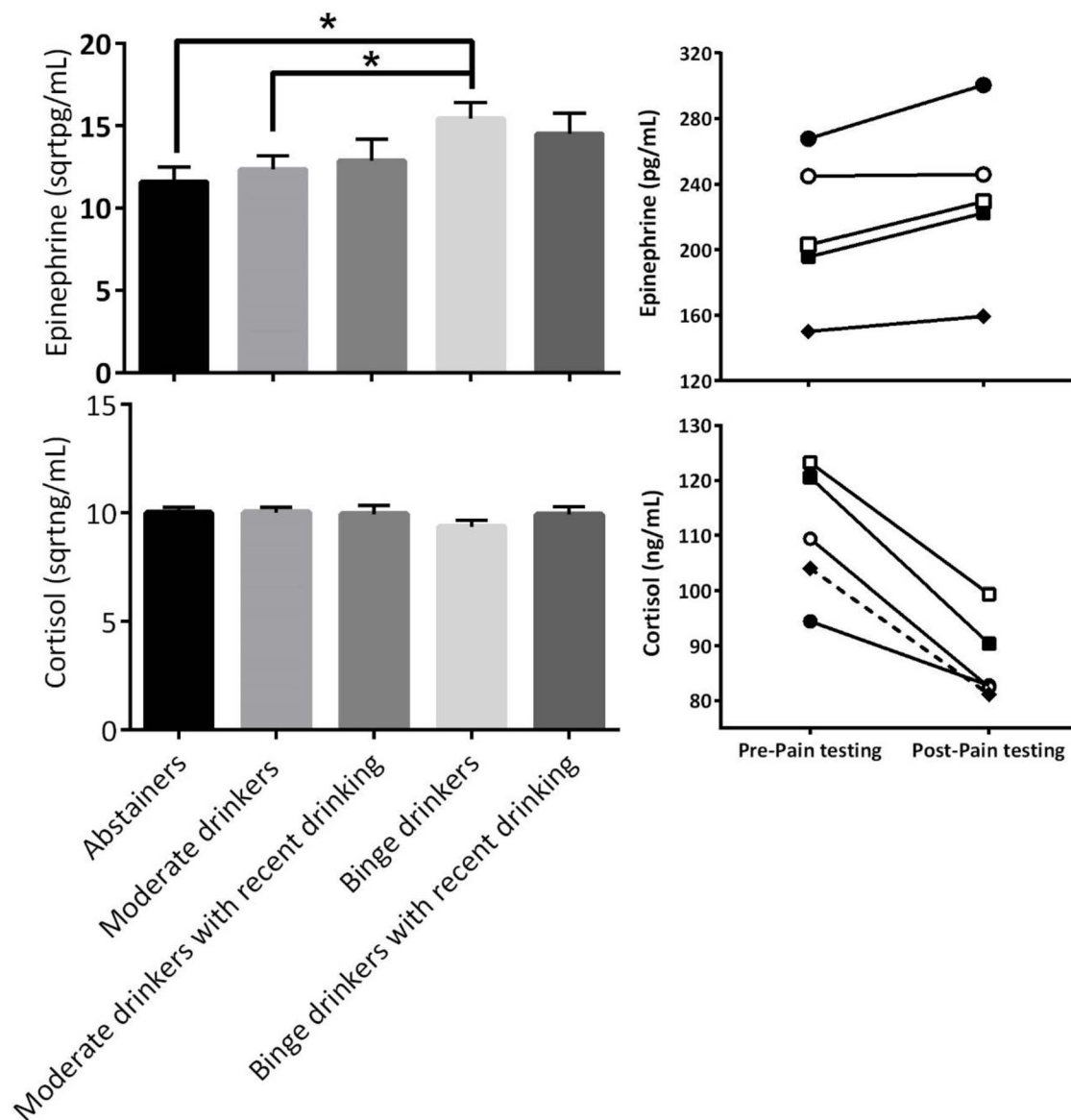


Fig. 3. Comparison of epinephrine (upper left) and cortisol concentrations (lower left) between the groups with different drinking patterns (Error bar = SEM).

Negative effect in relation to drinking patterns and pain sensitivity

Because baseline depressive symptoms were significantly higher in drinkers regardless of drinking patterns, no additional tests were conducted. No significant changes in STAI scores by the three QSTs were observed ($M = 0.07$, $SD = 2.42$), $P = 0.732$.

Physiological responses to pain testing

Changes in HR, SCL and RR were compared between the groups with a 3 (time: baseline, pain testing and final) by 5 (group) repeated measures ANOVA. Results revealed significant effects only on time, $P_s < 0.001$. LSD post-hoc analyses indicated that HR was elevated during pain testing ($M = 74.7$, $SD = 9.5$) and after pain testing ($M = 74.5$, $SD = 9.7$) compared to baseline ($M = 73.6$, $SD = 9.8$). Secondly, compared to baseline ($M = 2.3$, $SD = 0.7$), SCL was elevated during ($M = 2.8$, $SD = 0.6$) and after pain testing ($M = 2.7$, $SD = 0.6$). Thirdly, RRs were elevated during ($M = 14.9$, $SD = 2.3$)

and after pain testing ($M = 14.6$, $SD = 2.8$) compared to baseline ($M = 13.8$, $SD = 3.3$). A post-hoc test was conducted for SCL because a significant time by group interaction effect was observed, $F(5, 214) = 3.17$, $P = 0.009$. The results indicated that initially different SCLs were no longer different during, $P = 0.382$, and after pain testing, $P = 0.414$.

Taken together, psychophysiological responses to pain testing were similar across the groups and paralleled the lack of group differences observed in epinephrine and cortisol responses to pain testing.

DISCUSSION

This study was the first to examine whether hyperalgesia would occur within 2 days of drinking in young adult episodic binge drinkers. We also examined whether this hyperalgesia would be associated with epinephrine and cortisol hormones or negative effect. Our results indicated that hypersensitivity to muscle pressure pain

occurred in episodic binge drinkers who reported drinking within 2 days and experiencing acute alcohol withdrawal symptoms at the time of testing. Specifically, PPTs were lower in binge drinkers with recent drinking compared to binge drinkers without it. Therefore, hyperalgesia may occur in episodic binge drinkers during withdrawal. Hypersensitivity to muscle pressure pain was also observed in episodic binge drinkers without recent drinking compared to the moderate drinkers without recent drinking. Yet, binge drinking was not associated with persistent hyperalgesia, as muscle pressure thresholds were not significantly different between abstainers and binge drinkers without recent drinking. Cutaneous mechanical and heat pain thresholds were not associated with binge drinking and alcohol withdrawal. Next, binge drinking was associated with an elevation of plasma epinephrine concentration, but alcohol withdrawal was not associated with its further elevation. In contrast, plasma cortisol concentrations were unrelated to binge drinking and alcohol withdrawal. Finally, we did not find significant group differences in psychological distress levels with one exception. Binge and moderate drinkers reported more depressive symptoms compared to abstainers, suggesting depressive symptoms were associated with alcohol use.

We found that alcohol withdrawal was associated with transitory hypersensitivity to muscle pressure pain, consistent with findings in rodents (Gatch and Lal, 1999; Dina *et al.*, 2000, Dina *et al.*, 2006, Dina *et al.*, 2008). Our finding is also consistent with previous human research showing reversible withdrawal-associated hyperalgesia in alcohol-dependent men (Jochum *et al.*, 2010). This study extends that work by showing that hypersensitivity to muscle pressure pain may occur during alcohol withdrawal periods even in healthy young adults with only 2–3 years of episodic binge drinking history. With persistent binge drinking, persistent hyperalgesia may develop (Chopra and Tiwari, 2012) as subjective symptoms of alcoholic neuropathy are reported by 20% of alcoholics during the first 5 years of misuse and 40% after 10 years (Vittadini *et al.*, 2001). Thus, future studies could explore the development of alcohol withdrawal-associated hyperalgesia from transitory to persistent.

Rodent studies show that the stress axes can mediate alcohol withdrawal-induced hyperalgesia (Dina *et al.*, 2006; Dina *et al.*, 2008). Our findings suggest that some of these preclinical findings translate to humans, as epinephrine was elevated in binge drinkers regardless of recent drinking. Therefore, elevated epinephrine in binge drinking may be related to binge drinking-associated with hyperalgesia and explained some of the variance in withdrawal-induced hyperalgesia, albeit only to a small degree (7%). Although we found no further elevation of epinephrine levels with alcohol withdrawal symptoms, others observed elevated epinephrine and norepinephrine levels during alcohol withdrawal (Hawley *et al.*, 1981; Heikkonen *et al.*, 1989; Patkar *et al.*, 2003). Evidence linking HPA axis activation to drinking is mixed. Some observed elevated cortisol levels during withdrawal (Adinoff *et al.*, 1991; Adinoff *et al.*, 2003), whereas others observed blunted cortisol levels in young adult binge drinkers (Orio *et al.*, 2018). We found no group differences in cortisol levels. The inconsistency between ours and other studies is potentially due to differences in the time after the last drinking, the number of years of alcohol use and age of the drinkers. This study defined the window of alcohol withdrawal to include the period up to 48 h after the last drink. Despite withdrawal symptoms, epinephrine and cortisol levels might be recovered in our healthy young adults who engaged in episodic binge drinking. Additionally, the role of stress hormones may be more pronounced in the forced ethanol diet used in rodent studies (Dina *et al.*, 2006, Dina *et al.*, 2008). Indeed, a mouse study showed that after a voluntary ethanol diet, withdrawal-induced hyperalgesia occurred without elevation of corticosterone levels (Smith *et al.*,

2016). However, even in the case of self-administration, blocking the signaling pathway of corticotropin release reduced hyperalgesia in ethanol-dependent rats (Edwards *et al.*, 2012), suggesting cortisol may play a role in later stages of drinking.

Unexpectedly, we did not observe greater negative effect in binge relative to moderate drinkers. Drinkers reported slightly higher depressive symptoms compared to abstainers. Previous findings are mixed, with some finding an association between college binge drinking and depression (Cranford *et al.*, 2009) and others finding a U-shaped pattern, with abstainers and heavy drinkers reporting more depressive symptoms than moderate drinkers (O'Donnell *et al.*, 2006) or no association (Dawson *et al.*, 2005; Geisner *et al.*, 2012). Our null finding in negative effect may be due to our exclusion of individuals with psychiatric diagnoses or treatments. Therefore, binge drinkers in this study may be different from typical college binge drinkers.

Limitations of the current study should be acknowledged. First, we were unable to recruit an equal number of men and women to control for potential sex differences. Therefore, the absence of sex effects in this study may be due to insufficient power. Additionally, participants' self-reported last drinking episode might be inaccurate because it was based on recall. However, the binge drinkers who endorsed drinking within 2 days reported greater acute hangover symptoms at the time of experiment compared to binge drinkers who endorsed no recent drinking and moderate drinkers. Therefore, endorsement of recent drinking was consistent with acute hangover symptoms. Future studies could assess a biomarker (e.g. phosphatidylethanol) to verify self-reported alcohol consumptions (Schröck *et al.*, 2017). More importantly, natural drinking allows to study the effect of 'typical' alcohol withdrawal on pain sensitivity ethically in young adult binge drinkers, and their typical binge drinking was far greater than the minimum binge drinking definition (White *et al.*, 2006). Therefore, our study design has greater external validity. Lastly, this between subject-design was limited in examining the effect of alcohol withdrawal on pain sensitivity because of unknown individual differences in pain sensitivity at baseline.

In summary, this was the first study to demonstrate that alcohol withdrawal-associated hyperalgesia to muscle pressure pain existed in young adult binge drinkers. Additionally, elevated basal concentration of epinephrine was associated with binge drinking. However, cortisol concentration and negative effect were unrelated to either binge drinking or alcohol withdrawal. Additional studies are warranted to disentangle the role and the timeline of stress hormones and negative effect in alcohol withdrawal-induced hyperalgesia.

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CONFLICT OF INTEREST STATEMENT

None declared.

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