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EFFECT OF INTRAVENOUS ETHANOL ON CAPSAICIN INDUCED HYPERALGESIA IN HUMAN SUBJECTS

Caroline A. Arout, Ph.D.^a, Albert C. Perrino Jr., M.D.^b, Elizabeth Ralevski, Ph.D.^a, Gregory Acampora, M.D.^c, Julia Koretski, B.A.^a, Diana Limoncelli, B.A.^a, Jenelle Newcomb, B.A.^a, and Ismene L. Petrakis, M.D.^a

^aDepartment of Psychiatry, Center for Translational Neuroscience of Alcoholism and VA Alcohol Research Center

^bDepartment of Anesthesiology, Yale University School of Medicine, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516

^cDepartment of Psychiatry, Massachusetts General Hospital, Harvard Center for Addiction Medicine, 55 Fruit Street, Boston, MA 02114

Abstract

Background—The objective of this study was to assess ethanol's effects on capsaicin induced hyperalgesia in healthy participants. Specifically, we investigated the change in area of capsaicin induced hyperalgesia following three interventions: intravenous ethanol at two targeted breath alcohol concentrations (BrAC), or placebo.

Methods—Eighteen participants participated in 3 test days in a randomized order. Each test day, participants received an intradermal capsaicin injection on the volar surface of the forearm, followed by either infusion of high concentration ethanol (targeted BrAC = 0.100 g/dl), low concentration ethanol (targeted BrAC = 0.040 g/dl), or placebo. The area of hyperalgesia was determined by von Frey technique at two time points; prior to ethanol infusion, and again when target BrAC was reached. The primary outcome was the percent change in the area of capsaicin induced hyperalgesia. Additional outcome measures included the Visual Analogue Scale of mood states (VAS), which was administered at each time point.

Results—There was a marked 30% reduction in the area of capsaicin induced hyperalgesia with infusion of a high concentration of ethanol ($p < 0.05$). Low concentration ethanol produced a 10% reduction in hyperalgesia area, though this finding did not reach significance. Further, participants reported significant feelings of euphoria and drowsiness at high concentrations of ethanol ($p < 0.05$), as measured by the VAS.

Conclusion—In a human model examining pain phenomena related to central sensitization, the current study is the first to demonstrate that capsaicin induced hyperalgesia is markedly

Corresponding author: Caroline A. Arout, Ph.D., Yale University School of Medicine, VA Connecticut Healthcare System, Department of Psychiatry, 950 Campbell Avenue (116A), West Haven, CT 06516, Tel: (203) 932-5711 ext. 2796, Fax: (203) 937-3886, Caroline.Arout@yale.edu.

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attenuated by ethanol. The capsaicin experimental pain paradigm employed provides a novel approach to evaluate ethanol's effects on pain processing. The antihyperalgesic effects of ethanol observed have important clinical implications for the converging fields of substance abuse and pain medicine, and may inform why patients with chronic pain often report alcohol use as a form of self-medication.

Keywords

ethanol; hyperalgesia; capsaicin; pain; analgesia

Introduction

Chronic pain syndromes are of great clinical importance, as they are difficult to treat. Further, opioids, which are the mainstay of treatment for moderate to severe pain, have questionable efficacy when used chronically and in fact may worsen pain (Arout et al., 2015, Sullivan and Howe, 2013). Sensitization of central nervous system neurons is believed to be a neural substrate of chronic pain syndromes. In terms of nociception, central sensitization refers to increased synaptic transmission in subcortical somatosensory neurons, resulting in pain hypersensitivity to noxious stimuli (hyperalgesia) as well as pain to formerly innocuous stimuli (allodynia) (Latremoliere and Woolf, 2009, Woolf, 2011). Of particular clinical interest is the role of *N*-methyl-D-aspartate (NMDA) receptor binding, as studies have shown antagonists of this receptor to be effective in attenuating experimental pain (for a review of this literature, please see (Staahl et al., 2009b).

Ethanol has been shown to have analgesic properties in humans (Mullin and Luckhardt, 1934, Wolff et al., 1941, Cutter et al., 1976, James et al., 1978), and its effects on acute pain are comparable to the pain-relieving effects of opioid analgesics (Woodrow and Eltherington, 1988). Most recently, using an intravenous (IV) clamp infusion technique, our group demonstrated a breath alcohol concentration (BrAC) dependent analgesic effect of ethanol in healthy subjects using noxious electrical stimulation (Perrino et al., 2008, Ralevski et al., 2010).

Notably, no previous investigations evaluated ethanol's ability to modulate central sensitization and hyperalgesia. As NMDA glutamate receptors have been identified as neural substrates of ethanol (Krystal et al., 2003, Holmes et al., 2013, Zhao et al., 2015), we hypothesize ethanol to be a candidate agent to attenuate central sensitization and chronic pain. Laboratory studies in mice support this contention, showing partial blockade of ethanol analgesia with the NMDA receptor antagonist MK-801 (Mogil et al., 1993).

To examine ethanol's anti-hyperalgesic properties, we designed a double-blind, randomized, placebo-controlled investigation in healthy human participants. The protocol employed a clamped infusion of IV ethanol, and an intradermal capsaicin model to induce central sensitization. Capsaicin causes a long-lasting state of primary and secondary hyperalgesia mediated by central sensitization of glutamatergic neurons of the spinal dorsal horn (Staahl and Drewes, 2004, Staahl et al., 2009b, Staahl et al., 2009a, Winter et al., 1995, Woolf, 2011). The use of capsaicin induced pain as an experimental paradigm provides a unique perspective, as its central mechanism of action closely mimics the neurophysiology observed

in clinical chronic pain states (Staahl et al., 2009a, Balabathula et al., 2014), and it has been useful in understanding the analgesic properties of medications (Park et al., 1995).

We hypothesized that capsaicin induced hyperalgesia would be attenuated by ethanol; as such, this experimental pain paradigm may provide new insights towards understanding ethanol's effects.

Material and Methods

Subject Selection

Healthy volunteers (n = 18) were recruited by advertisement for the current study, which was approved by the institutional review board. After signing informed consent, participants underwent baseline screening, including medical and psychiatric examination, and then an orientation session that included a "trial" capsaicin injection, so as to familiarize patients with the paradigm. All participants were compensated for their participation.

Inclusion criteria specified participants who were: (i) males and females between the ages of 21 and 30 years; (ii) medically and neurologically healthy as determined by evaluation of history, physical examination, and screening laboratories. Exclusion criteria included those who/with: (i) met DSM-IV criteria for diagnosis of a psychiatric or substance abuse disorder (excluding alcohol abuse) as determined by psychiatric evaluation and confirmed by a structured diagnostic interview (Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)); (ii) were alcohol naïve; (iii) for women, a positive pregnancy test at screening or an intention to engage in unprotected sex during the study.

Study Design

This study utilized a double-blind, placebo-controlled, within-subjects design in which participants were randomly assigned to two conditions of IV ethanol and placebo administration on three separate test days in random order, minimally three days apart. Test days included infusion of low concentration ethanol (targeted BrAC = 0.040 g/dl; approximately 2 drinks), high concentration ethanol (targeted BrAC = 0.100 g/dl; approximately 5 drinks), or placebo (saline solution). Double-blind procedures were insured using independent research and nursing personnel; thus, raters and participants alike remained blind to BrAC levels during all sessions. While the nursing staff were not blind, they did not interact with the research staff so as to maintain blinded conditions. All testing was carried out in the Biological Studies Unit at the VA Connecticut Healthcare System, West Haven campus.

Ethanol Infusion

IV infusion (6% ethanol by volume in 0.9% saline) was delivered via computerized pump (Braun Horizon NXT) in order to achieve a predetermined, steady target BrAc. The IV method of ethanol infusion is well-established (Ramchandani et al., 1999, Subramanian et al., 2002, O'Connor et al., 1998) and is described in detail elsewhere (Perrino et al., 2008). The objective is to reach a targeted ethanol concentration (measured in BrAC) at a rate which is individualized for age, sex, and weight in approximately 20 minutes, to be

maintained for the following 60 minutes. After the target BrAC is reached, the ethanol infusion is “clamped” and maintained at the specified level (± 5 g/dl) for 60 minutes. Nursing staff made any necessary adjustments based on BrAC. On placebo day, the IV bags were identical, and the procedure was matched to that of the ethanol infusion days.

Pain Testing: Intradermal Capsaicin

Capsaicin (Sigma-Aldrich) was injected once on each test day, 15 minutes prior to the start of ethanol or placebo infusion. Capsaicin was dissolved in a vehicle of 5% Tween-80 in sterile, phosphate-buffered saline (pH = 7.4) to achieve target strength per volume. For each intradermal injection, a volume of 25 μ l consisting of 250 μ g capsaicin was administered into the volar surface of the forearm via a 29g needle. Pain assessments were performed at two time points on each test day, both prior to the start of placebo/ethanol infusion (baseline) and once the predetermined target BrAC was reached (target; approximately 40 minutes post-capsaicin injection).

Intradermal capsaicin injection produces areas of long lasting primary and secondary hyperalgesia, which are mediated by C- and A δ fibers, followed by A β -regulated allodynia. These states of increased sensitivity are quantified by von Frey filaments, which assess sensory threshold by producing quantified, light pressure via a pinprick sensation (Stahl and Drewes, 2004). A previous study showed this pink-prick hyperalgesia, though gradually diminishing, lasts minimally 13 hours (LaMotte et al., 1991). In the current study, the hyperalgesic field was mapped using a 20.9g von Frey filament along eight linear paths arranged radially around the stimulation site, in 5mm steps and 1s intervals. The stimulation along each path was initiated beyond the anticipated hyperalgesic area, and was continued inward until the subject reported a marked change in the magnitude of nociceptive sensations (i.e. burning, tenderness, more intense pricking). The point on the skin at which the subject reported an increase in pain was marked with pen, and after all 8 points were determined, a digital photograph was taken. The photograph was then analyzed by way of an off-line computer analysis package, which allowed for planimetry of the pen marks and calculation of the encompassed hyperalgesic surface area in cm². The primary outcome measure was the percent change in capsaicin induced hyperalgesic area, from that measured before infusion to target BrAc.

Subjective Measures of Ethanol Effects

A range of stimulant and sedative effects of ethanol were evaluated using the Visual Analogue Scale of mood states (VAS). The VAS used was a 10-item self-report scale containing descriptive words that assessed the euphoric effects of ethanol including “buzzed” and “high”, and other subjective effects including “drowsy”, where participants were asked to rate, on a scale of 0 to 7, the extent to which they were experiencing such feelings at the present moment. This scale is sensitive to ethanol effects and has been shown to have good convergent validity with similar scales. In the current study, the VAS was completed at approximately the same time that pain assessments were completed, both pre-infusion and at target BrAc, to examine the alcohol effects experienced by participants.

Statistical Analyses

To test our hypothesis, we used IBM's Statistical Package for the Social Sciences (SPSS) to run a repeated measures ANOVA to examine change in capsaicin induced hyperalgesic area following placebo, low concentration, or high concentration ethanol infusion, as measured by BrAC. The primary outcome measure was the percent change in capsaicin induced hyperalgesic area (cm²) as a function of BrAC. Post hoc analyses assessed differences in responses as a function of BrAC.

Results

Demographic Characteristics

A total of 18 subjects (10 males, 8 females) participated in this study. Subjects were between the ages of 21 and 30 ($M = 24.11 \pm 2.89$) and were well educated (16.39 ± 2.25 years of education). They reported low levels of drinking within the previous 30 days of study enrollment (M number of drinking days = 5.44 ± 3.45 ; M total number of drinks = 15.72 ± 14.34). One participant enrolled in this study was diagnosed with lifetime alcohol abuse due to familial objection, though was healthy at the time of study enrollment.

Ethanol Impact on Capsaicin Induced Hyperalgesia

Analyses revealed a significant effect of ethanol on area of capsaicin induced hyperalgesia ($F(2, 26) = 6.36, p = 0.006$). Specifically, ethanol reduced the capsaicin induced hyperalgesic response by nearly 30% during infusion at the targeted high BrAC of 0.100 g/dl ($p = 0.001$ when compared to placebo; Figure 1). The lower ethanol BrAC (target of 0.040 g/dl) produced substantial reductions in the area of hyperalgesia of over 10% when compared to placebo. However, this difference was not significant when compared to the reduction occurring during placebo infusion ($p = 0.289$; Figure 1).

Subjective Effects

To confirm that the ethanol clamp infusion procedure used in this study resulted in administration of the targeted ethanol BrAC, the BrAC was recorded for each subject. For the low (0.040 g/dl) and high (0.100 g/dl) concentrations of ethanol, the mean BrAC readings at target were 0.041 g/dl ($SD = 0.002$) and 0.102 g/dl ($SD = 0.003$), respectively.

To confirm that ethanol infusion resulted in subjective mood alterations, responses on the VAS were analyzed. Ethanol infusion at the high target BrAC altered participants' subjective mood responses, as indicated by feelings of euphoria and intoxication on the VAS. Specifically, participants reported feeling "buzzed", "high", and "drowsy" in the high ethanol BrAC condition ($p < 0.05$; Figure 2). These subjective effects were also reported at a lower intensity during the low concentration ethanol infusion, although they did not reach statistical significance ($p > 0.05$; Figure 2). Though this illustrates that infusion of a high concentration of ethanol results in significant alcohol effects, no correlation was found between the subjective mood effects of ethanol and pain responses.

Discussion

The results of this study demonstrate that ethanol administration in laboratory subjects attenuates capsaicin induced hyperalgesia. High concentration ethanol reduced the area of hyperalgesia by nearly 30% when compared to placebo ($p < 0.05$), while low concentration ethanol resulted in a reduction of capsaicin induced hyperalgesia of over 10%, although the latter did not reach statistical significance. These analgesic effects mirror the subjective effects observed, where high concentration ethanol showed a significant increase in subjective effects (i.e., “buzzed”, “high”, and “drowsy”), and the low concentration showed an increase in these factors that was not statistically significant.

Patients with chronic pain states often report hypersensitivity to touch and painful stimuli. This clinical phenomenon involves the same mechanism as the hypersensitivity experienced with intradermal capsaicin injection. As such, the use of the capsaicin paradigm has been important in the study of pain related to central sensitization, and to evaluate treatment modalities for this condition. For example, the NMDA antagonist ketamine has been widely examined as pharmacologic treatment for central sensitization pain states and is frequently employed to manage hyperalgesia in chronic pain and post-surgical patients, both conditions where central sensitization is a causative factor (Staahl et al., 2009b, Arout et al., 2015, Radvansky et al., 2015, Pozek et al., 2016). The results of the current study suggest the antihyperalgesic effects of ethanol are equally as potent as other NMDA antagonists. Specifically, the magnitude of the antihyperalgesia observed in this study is similar to that found in prior studies assessing ketamine’s antihyperalgesic effects using a similar intradermal capsaicin methodology (Park et al., 1995, Sethna et al., 1998). These findings also complement previous findings from our group, which demonstrated, using an identical clamped infusion technique, that both high and low concentrations of ethanol have analgesic effects on acute pain from noxious electrical stimulation (Perrino et al., 2008, Ralevski et al., 2010). Electrical stimulation differs from intradermal capsaicin, in that it directly activates the nerve, bypassing nociceptors in the skin, and is mediated by peripheral afferent A β , A δ , and unmyelinated C fibers. This paradigm yields an acute measure of pain threshold and pain tolerance through activation of the NMDA receptor, though its clinical relevance remains undetermined due to this global, nonspecific mechanism of action (Staahl et al., 2009a, Olesen et al., 2012).

A limitation of the current study is the small sample size ($n=18$); a larger sample size may have provided adequate statistical power to differentiate the antihyperalgesia produced by low concentration ethanol. The study is also limited by the homogeneity of the subject population. Investigating the influence of other demographic variables such as variations in family history of alcoholism and sex differences may highlight important clinical implications. Extending this study to evaluate other populations, such as those with chronic pain syndromes or alcohol use disorders would be of great clinical interest.

Our findings have clinical relevance, both in substance abuse and pain medicine disciplines. The potent antihyperalgesic effect of ethanol may inform why as many as 25% of chronic pain patients report using ethanol as a form of self-medication for their pain (Riley and King, 2009), as well as the high rates of comorbidity seen with chronic pain and alcohol use

disorders (Egli et al., 2012). In fact, one study indicated that 58% of a sample of problem drinkers were using alcohol to manage their moderate to severe pain, as compared to 21% of non-problem drinkers (Brennan et al., 2005). Ethanol's profile of deleterious effects precludes its recommendation as a prescribed therapeutic analgesic. Similarly, opioid therapies have serious drawbacks, including addiction, and lack efficacy for chronic pain (Sullivan and Howe, 2013). Development of non-opioid regimens for chronic pain is of high clinical importance, both for the management of painful conditions, and to avert the scourge of ethanol and opioid use disorders related to pain. The capsaicin paradigm is a useful tool in this development, and has been employed to examine prospective analgesic therapies including magnesium (Mikkelsen et al., 2001, Lee and Ryan, 2003), gabapentin (Gottrup et al., 2004, Dirks et al., 2002), and ketamine (Park et al., 1995, Sethna et al., 1998).

In summary, the current study is the first to demonstrate that capsaicin induced hyperalgesia is markedly attenuated by ethanol. These findings have important implications both for substance abuse and pain medicine disciplines.

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References

- Arout CA, Edens E, Petrakis IL, Sofuoglu M. Targeting Opioid-Induced Hyperalgesia in Clinical Treatment: Neurobiological Considerations. *CNS Drugs*. 2015;1–22. [PubMed: 25380674]
- Balabathula P, Bhattacharjee H, Thoma LA, Nolly RJ, Horton FP, Stornes GD, Wan JY, Brooks IM, Bachmann GA, Foster DC, Brown CS. Potency and Stability of Intradermal Capsaicin: Implications for Use as a Human Model of Pain in Multicenter Clinical Trials. *Clin Exp Pharmacol*. 2014; 4:142. [PubMed: 25105064]
- Brennan PL, Schutte KK, Moos RH. Pain and use of alcohol to manage pain: prevalence and 3-year outcomes among older problem and non-problem drinkers. *Addiction*. 2005; 100:777–786. [PubMed: 15918808]
- Cutter HS, Maloof B, Kurtz NR, Jones WC. "Feeling no pain" differential responses to pain by alcoholics and nonalcoholics before and after drinking. *Journal of studies on alcohol*. 1976; 37:273–277. [PubMed: 4661]
- Dirks J, Petersen KL, Rowbotham MC, Dahl JB. Gabapentin suppresses cutaneous hyperalgesia following heat-capsaicin sensitization. *Anesthesiology*. 2002; 97:102–107. [PubMed: 12131110]
- Egli M, Koob GF, Edwards S. Alcohol dependence as a chronic pain disorder. *Neuroscience & Biobehavioral Reviews*. 2012; 36:2179–2192. [PubMed: 22975446]
- Gottrup H, Juhl G, Kristensen AD, Lai R, Chizh BA, Brown J, Bach FW, Jensen TS. Chronic oral gabapentin reduces elements of central sensitization in human experimental hyperalgesia. *Anesthesiology*. 2004; 101:1400–1408. [PubMed: 15564948]

- Holmes A, Spanagel R, Krystal JH. Glutamatergic targets for new alcohol medications. *Psychopharmacology (Berl)*. 2013; 229:539–554. [PubMed: 23995381]
- James M, Duthie A, Duffy B, McKeag A, Rice C. Analgesic effect of ethyl alcohol. *British journal of anaesthesia*. 1978; 50:139–141. [PubMed: 341934]
- Krystal JH, Petrakis IL, Mason G, Trevisan L, D'Souza DC. N-methyl-D-aspartate glutamate receptors and alcoholism: reward, dependence, treatment, and vulnerability. *Pharmacol Ther*. 2003; 99:79–94. [PubMed: 12804700]
- LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *J Neurophysiol*. 1991; 66:190–211. [PubMed: 1919666]
- Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009; 10:895–926. [PubMed: 19712899]
- Lee DC, Ryan JR. Magnesium–Aluminum Hydroxide Suspension for the Treatment of Dermal Capsaicin Exposures. *Academic emergency medicine*. 2003; 10:688–690. [PubMed: 12782534]
- Mikkelsen S, Dirks J, Fabricius P, Petersen K, Rowbotham M, Dahl J. Effect of intravenous magnesium on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers. *British journal of anaesthesia*. 2001; 86:871–873. [PubMed: 11573598]
- Mogil JS, Marek P, Yirmiya R, Balian H, Sadowski B, Taylor AN, Liebeskind JC. Antagonism of the non-opioid component of ethanol-induced analgesia by the NMDA receptor antagonist MK-801. *Brain research*. 1993; 602:126–130. [PubMed: 8448649]
- Mullin F, Luckhardt A. The effect of alcohol on cutaneous tactile and pain sensitivity. *American Journal of Physiology*. 1934:109.
- O'Connor S, Morzorati S, Christian J, Li TK. Clamping breath alcohol concentration reduces experimental variance: application to the study of acute tolerance to alcohol and alcohol elimination rate. *Alcoholism: Clinical and Experimental Research*. 1998; 22:202–210.
- Olesen AE, Andresen T, Staahl C, Drewes AM. Human experimental pain models for assessing the therapeutic efficacy of analgesic drugs. *Pharmacological reviews*. 2012; 64:722–779. [PubMed: 22722894]
- Park KM, Max MB, Robinovitz E, Gracely RH, Bennett GJ. Effects of intravenous ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin in human subjects. *Pain*. 1995; 63:163–172. [PubMed: 8628581]
- Perrino AC, Ralevski E, Acampora G, Edgecombe J, Limoncelli D, Petrakis IL. Ethanol and pain sensitivity: effects in healthy subjects using an acute pain paradigm. *Alcoholism: Clinical and Experimental Research*. 2008; 32:952–958.
- Pozek J-PJ, Beausang D, Baratta JL, Viscusi ER. The Acute to Chronic Pain Transition: Can Chronic Pain Be Prevented? *Medical Clinics of North America*. 2016; 100:17–30. [PubMed: 26614716]
- Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, Eloy JD. Role of Ketamine in Acute Postoperative Pain Management: A Narrative Review. *Biomed Res Int*. 2015; 2015:749837. [PubMed: 26495312]
- Ralevski E, Perrino A, Acampora G, Koretski J, Limoncelli D, Petrakis I. Analgesic effects of ethanol are influenced by family history of alcoholism and neuroticism. *Alcoholism: Clinical and Experimental Research*. 2010; 34:1433–1441.
- Ramchandani VA, Bolane J, Li TK, O'Connor S. A Physiologically-Based Pharmacokinetic (PBPK) Model for Alcohol Facilitates Rapid BrAC Clamping. *Alcoholism: Clinical and Experimental Research*. 1999; 23:617–623.
- Riley JL, King C. Self-report of alcohol use for pain in a multi-ethnic community sample. *The Journal of Pain*. 2009; 10:944–952. [PubMed: 19712901]
- Sethna NF, Liu M, Gracely R, Bennett GJ, Max MB. Analgesic and cognitive effects of intravenous ketamine-alfentanil combinations versus either drug alone after intradermal capsaicin in normal subjects. *Anesth Analg*. 1998; 86:1250–1256. [PubMed: 9620514]
- Staahl C, Drewes AM. Experimental human pain models: a review of standardised methods for preclinical testing of analgesics. *Basic & clinical pharmacology & toxicology*. 2004; 95:97–111. [PubMed: 15447733]

- StaaHL C, Olesen AE, Andresen T, Arendt-Nielsen L, Drewes AM. Assessing analgesic actions of opioids by experimental pain models in healthy volunteers—an updated review. *British journal of clinical pharmacology*. 2009a; 68:149–168. [PubMed: 19694733]
- StaaHL C, Olesen AE, Andresen T, Arendt-Nielsen L, Drewes AM. Assessing efficacy of non-opioid analgesics in experimental pain models in healthy volunteers: an updated review. *British journal of clinical pharmacology*. 2009b; 68:322–341. [PubMed: 19740390]
- Subramanian MG, Heil SH, Kruger ML, Collins KL, Buck PO, Zawacki T, Abbey A, Sokol RJ, Diamond MP. A Three-Stage Alcohol Clamp Procedure in Human Subjects. *Alcoholism: Clinical and Experimental Research*. 2002; 26:1479–1483.
- Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: Promises and perils. *PAIN®*. 2013; 154(Supplement 1):S94–S100. [PubMed: 24036286]
- Winter J, Bevan S, Campbell E. Capsaicin and pain mechanisms. *British Journal of Anaesthesia*. 1995; 75:157–157. [PubMed: 7577249]
- Wolff HG, Hardy JD, Goodell H. Measurement of the effect on the pain threshold of acetylsalicylic acid, acetanilid, acetophenetidin, aminopyrine, ethyl alcohol, trichlorethylene, a barbiturate, quinine, ergotamine tartrate and caffeine: an analysis of their relation to the pain experience. *Journal of Clinical Investigation*. 1941; 20:63. [PubMed: 16694809]
- Woodrow KM, Eltherington LG. Feeling no pain: alcohol as an analgesic. *Pain*. 1988; 32:159–163. [PubMed: 3362554]
- Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *PAIN*. 2011; 152:S2–S15. [PubMed: 20961685]
- Zhao Y, Ren H, Dwyer DS, Peoples RW. Different sites of alcohol action in the NMDA receptor GluN2A and GluN2B subunits. *Neuropharmacology*. 2015; 97:240–250. [PubMed: 26051400]

Figure 1.

Percent change in capsaicin induced area of hyperalgesia as a function of ethanol (placebo, low BrAC, or high BrAC). Data represent means $\pm$ SEM (N = 18). * $p < 0.05$ as compared to placebo for each respective condition.

Figure 2.

Visual Analog Scale of mood states. The top figure represents the “buzzed” and “high” items, averaged to illustrate the euphoric effects of ethanol. The bottom figure represents the VAS “drowsy” item. Data represent mean scores at each time point (represented in minutes following the start of infusion) for placebo, low BrAC (Low), and high BrAC (High) ethanol conditions, $\pm$ SE. Participants reported significant alcohol effects following infusion of a high concentration of ethanol (* $p < 0.05$).

Table 1

Demographic Characteristics

Variable	<i>M(SD)</i>
Age	24.11 (2.89)
Total drinking days	5.44 (3.45)
Total number of drinks (past 30 days)	15.72 (14.34)
Years of education	16.39 (2.25)
Age at first drink	17 (1.78)