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ORIGINAL ARTICLE

Alcohol-triggered signs of migraine: An animal model

Yaqoub Alabwah[a], Yadong Ji[a], David A. Seminowicz[b,c], Raimi L. Quiton[b,d,e] and Radi Masri[a,c,e]

[a]Department of Endodontics, Prosthodontics and Operative Dentistry, University of Maryland School of Dentistry, Baltimore, MD, USA; [b]Department of Neural and Pain Sciences, University of Maryland School of Dentistry, Baltimore, MD, USA; [c]Program in Neuroscience, University of Maryland, Baltimore, MD, USA; [d]Department of Psychology, University of Maryland, Baltimore County, Baltimore, MD, USA; [e]Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD, USA

ABSTRACT

We describe an animal model where characteristics of migraine can be triggered by alcohol administration. In rats chronically implanted with a cannula overlying the transverse sinus, we applied potassium chloride (KCl) (or saline) to the meninges to sensitize trigeminovascular afferents. We assessed effects of repeated KCl application on animal behavior using conditioned place avoidance paradigm. In KCl-treated rats we discovered that alcohol injections (0.2 mg/kg), but not saline, resulted in the development of extracephalic allodynia and signs of ongoing pain.

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Migraine; headache; trigeminal

Introduction

Migraine is a recurring, moderate to severe, unilateral, throbbing, disabling, primary headache that can last for hours to days (Goadsby et al. 2002). Migraine headaches may be associated with aura, photophobia (hypersensitivity to light), phonophobia (hypersensitivity to sound), nausea, and a variety of autonomic, cognitive, emotional, and motor disturbances (Lipton et al. 2001). Approximately 60% of patients report migraine headache to be associated with pain in response to innocuous stimulation of the skin in the head region (cephalic allodynia) and body regions (extracephalic allodynia) (Lipton et al. 2008).

Migraine headaches depend both on the activation of peripheral trigeminovascular afferents and on dysfunction of central nervous system structures involved in the modulation of neuronal excitability and pain such as the spinal trigeminal nucleus, the hypothalamus, the posterior thalamic complex, the somatosensory cortex, and cingulate cortex (Kagan et al. 2013; Noseda and Burstein 2013; Moulton et al. 2014). Repeated migraine attacks and repeated activation of trigeminovascular afferents result in maladaptive plastic changes or sensitization along the trigeminovascular afferent pathway, peripherally and centrally. This sensitization forms the basis for cephalic and extracephalic allodynia in migraineurs (Jakubowski et al. 2005; Burstein et al. 2010) and may render patients more susceptible to migraine triggers.

A wide variety of factors may trigger migraine headaches, such as alcohol, stress, hormonal fluctuations, sleep disturbances, diet, skipping meals, or sensory overload (Pavlovic et al. 2014). Alcohol has been identified as a trigger in as high as 75% of episodic migraineurs (Van den Bergh et al. 1987; Chabriat et al. 1999; Millichap and Yee 2003; Panconesi 2008), but also see Wober et al. (2007). The neural mechanisms underlying alcohol-triggered migraine attacks are unknown, due in part to the paucity of preclinical models that replicate distinct characteristics of this clinical condition (Dueland 2015).

Here, we use operant and behavioral tests of ongoing pain to test a novel animal model of alcohol-triggered headache that recapitulates key features of migraine. We hypothesized that repeated activation of meningeal afferents results in maladaptive plastic changes in the trigeminovascular system that are associated with increased sensitivity to alcohol, a common migraine trigger.

Methods

Animals

Twenty-three *Sprague-Dawley* rats (16 males and 7 females, 225–375 g; Harlan Laboratories, Indianapolis, IN, USA) were housed in ventilated plastic cages with soft bedding and maintained on a 12/12 h light/dark cycle (lights on at 07:00), at constant temperature (22 ± 2 °C) and humidity (50 ± 10%). Rats had access to standard rat chow and tap water *ad libitum*. Experiments were performed while animals were in their light cycle. All procedures were performed under an approved University of Maryland Baltimore IACUC (Institutional Animal Care and Use Committee) protocol.

Pharmaceutical agents

Potassium chloride (KCl) and saline (0.9% sodium chloride solution) were purchased from Sigma (St. Louis, MO). Alcohol

CONTACT R. Masri Radi.masri@gmail.com Department of Endodontics, Prosthodontics and Operative Dentistry, University of Maryland Dental School, 650 W Baltimore St. Office #6253, Baltimore, MD 21201, USA.

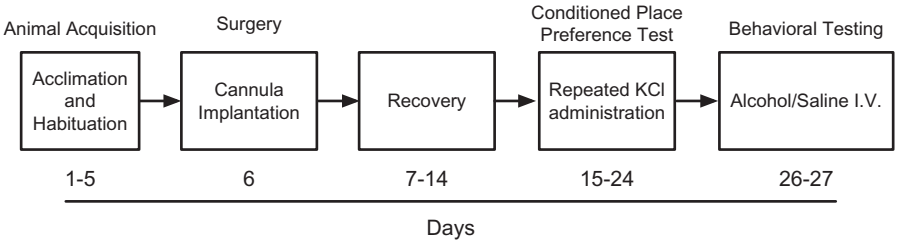

Figure 1. General experimental design timeline.

(ethyl alcohol, 200 proof) was purchased from Pharmaco-AAPER (Brookfield, CT).

General experimental design

The experimental design timeline is detailed in Figure 1. The animals were acclimated and habituated by handling the animals daily for 5 days before performing a survival surgery (details below) to implant a cannula for drug delivery onto the meninges. The animals were allowed to recover for 7 days after surgery before testing the effect of repeated meningeal application of KCl and saline on conditioned place preference/avoidance. Two days after the end of the test, the same animals received alcohol or saline through a tail vein (IV). Calibrated von Frey filaments and the rat Face Grimace Scale test (Sotocinal et al. 2011) were used for behavioral assessment, immediately after alcohol or saline injection (Figure 1).

Survival surgery

Strict aseptic surgical procedures were used in accordance with the University of Maryland's Guidelines. A presurgical assessment including weight, behavior, and signs of disease was conducted for each animal and recorded along with a detailed record of the surgical and post-surgical procedures.

Animals were anesthetized with isoflurane inhalant (3–5% initiation, 1.5–2.5% maintenance). Surgical sites were prepared by removing the hair with an electric clipper and wiped with 10% Betadine surgical scrub then 70% alcohol. An ocular protective lubricant was applied to the animal's eyes. The animal was then attached to a stereotaxic frame and placed on a thermo-regulated heating pad. Depth of anesthesia was determined every 15 min by monitoring pinch withdrawal, eyelid reflex, corneal reflex, respiration rate, and vibrissae movements. A long-acting local anesthetic (0.5% Marcaine) was applied to the surgical area to further reduce the possibility that animals could experience pain.

A longitudinal incision (10 mm) was performed using a #15 scalpel blade to expose the cranium. The skin and underlying periosteum were reflected using a periosteal elevator. An osteotomy (1 mm diameter) in the skull overlying the right transverse sinus (6.5 mm posterior and 3.0 mm lateral to bregma) was made using a manual drill (DH-0 Pin Vise; Small Parts, Logansport, IN, USA). A guide cannula 23 G (OD: 0.64 mm; ID: 0.32 mm) was loaded with a dummy probe to prevent obstruction of the guide cannula and inserted into the opening with caution, avoiding penetration of the meninges (depth: 1 mm). Two metal screws (TX00-2-C; Small Parts) were inserted proximal to the osteotomy site and the cannula guide was stabilized with the aid of dental resin. At the end of the survival surgery, the skin was closed with monofilament sutures (4-0, Vicryl). Animals recovered from anesthesia on a thermo-regulated pad, then were observed every 15 min before returning to their home cage. Rimadyl 5 mg/kg SQ was given before surgery and SID every 24 h for 48 h.

Application of medications to the meninges

To administer KCl or saline, the animals were restrained briefly using a custom-made black sock. The dummy cannula was removed and a Hamilton syringe (10 μl, 26s G) connected to a PE 10 tubing at one end and to an internal cannula 26 G (PlasticsOne, C312I/SPC) at the other end was inserted. KCl (1 M, 5 μl) or saline (5 μl; control) was administered slowly over a period of 1 min to the meninges overlying the transverse sinus. After the administration of medications, the cannula was removed and the dummy cannula was inserted back. Each animal ($n = 17$) received three applications of KCl and three applications of saline during testing for conditioned place preference/avoidance (details below).

Intravenous alcohol injection

Animals that had received repeated KCl and saline applications to the meninges were subsequently injected with 0.1 ml of saline or alcohol (0.2 g/kg), via the tail vein using a 25 G needle. Rats were placed into a custom cloth sack and gently restrained to inject alcohol. The tail was swabbed with an alcohol-dampened gauze and a warm pad (28–30 °C) was placed on the rat's tail for 5–10 min to dilate blood vessels. The needle was inserted into a lateral vein in the middle third of the tail. Aspiration was performed to confirm that the needle entered the vein before injecting alcohol (or saline) over a period of 1 min. Once the injection was completed, the needle was removed and slight pressure was applied to the injection site with dry gauze until the bleeding stopped. The same group of animals ($n = 14$) received alcohol or saline (control) injections on two consecutive days, in randomized order. On each day, mechanical hypersensitivity and face grimace measures were collected after injection (see "Behavioral Measures" below).

To test the effect of alcohol on animals that did not receive KCl applications, we used naive rats ($n = 6$) (no cannula implantation) rather than cannula-implanted rats that received repeated injections of saline. We reasoned that cannula implantation surgery and repeated administration of fluids onto the meninges is also likely to sensitize the meninges as has been reported in the literature (e.g., increased

calcitonin gene-related peptide (CGRP) expression due to control injections onto the dura (Stucky et al. 2011)), thus confounding our ability to test if alcohol-triggered behavioral changes are due to sensitization of the trigeminovascular system. Therefore, in naive rats, we injected alcohol (IV) as described above and assessed changes in mechanical withdrawal thresholds and Face Grimace Scale.

Behavioral tests

Conditioned place preference/avoidance paradigm. We used the conditioned place preference/avoidance paradigm (CPP) to test if KCl administration to meningeal afferents is aversive to animals. The CPP, which we have used in previous studies (Davoody et al. 2011), allows the animal to consciously decide to avoid the chamber it found uncomfortable without provocation (Carlezon 2003). Testing was conducted using a custom-built, automated two-chamber Plexiglas box, in which the walls of one chamber were lined with horizontal white and black stripes and the walls of the other chamber were lined with vertical white and black stripes.

First, we habituated the animals to the apparatus by allowing the animals to move freely for 30 min between the two chambers. This process was repeated over three consecutive days. On the fourth day, rats were permitted to move freely between the two chambers for 15 min and time spent in each chamber was recorded to determine each rat's preference.

After habituation and testing of baseline place preference, rats underwent a 3-day conditioning phase where KCl and saline were administered (5th, 6th and 7th day). Two sessions were conducted on each day, 4 h apart. In one session, the animals were placed for 90 min in the chamber that they demonstrated a preference for during the pre-conditioning test and KCl (1 M; 5 μl) was applied through the implanted cannula (as described above). In the other session, the animals were placed for 90 min in the chamber that they did not prefer during the pre-conditioning test and saline (5 μl) was delivered through the cannula. The order of injection was randomized. That is, some days the rat received saline in the first session while other days the rat received KCl in the first session. One day after the conditioning phase (8th day), a place preference/avoidance test was conducted in which rats received no drug treatment and were permitted to move freely between the two chambers for 15 min. Time spent in each chamber was recorded to determine each rat's chamber preference.

Mechanical hypersensitivity. Migraine headaches are accompanied by cephalic and extracephalic allodynia (Lipton et al. 2008). Therefore, we also used reflexive measures of hypersensitivity to gain insight on when signs of pain are occurring. This allowed us to optimize the period of video recording for face grimace testing (described below) as we were limited to 60 min of recording. This is because animals tend to rest and close their eyes in the recording chamber when recording periods extended beyond 60 min.

We focused on studying mechanical sensitivity of the hindpaw (extracephalic allodynia), and not mechanical sensitivity of the periorbital area (cephalic allodynia), because of the presence of a chronically implanted cannula in the head that is in close proximity to the area where cephalic allodynia is typically tested. Chronic implantation of cannula may significantly affect mechanical responses in the periorbital area.

Extracephalic allodynia in response to tail injection of alcohol (or saline) was assessed using calibrated von Frey filaments with circular plain tips (1.0–128.5 mN; diameter 0.1–0.25 mm). Rats were placed in a transparent Plexiglas chamber positioned on a wire mesh floor for testing and habituated for 15 min. Each stimulus consisted of a 2–3 s application of the von Frey probe to the middle of the plantar surface of the paw with a 1–2 min interval between stimuli. Left and right hindpaws were tested at least 20 times each. Quick withdrawal or licking of the paw in response to the stimulus was considered a positive response. We recorded both responses and non-responses. We calculated the force (threshold) at which the rat withdrew each hindpaw from the von Frey filament 50% of the time (Chaplan et al. 1994). If the animal showed no response to the von Frey probes, a value of 128.5 mN was assigned as threshold. Mechanical withdrawal thresholds were assessed when the animals were acquired (baseline, before any surgery), before alcohol or saline injections (preinjection), and at 30, 60, 90, 120, 180, and 240 min after injection on day 26 or 27. The examiner was blinded to whether alcohol or saline was injected on the testing day.

Rat Grimace Scale paradigm. Changes in Rat Grimace Scale in response to tail injection of alcohol (or saline) were assessed using similar methods to those previously described (Sotocinal et al. 2011). Animals ($n = 7$) sensitized with repeated administration of KCl (1 M; 5 μl, 3 times, administered during the conditioned place preference/avoidance paradigm) were placed individually in a transparent Plexiglas chamber. Two Sony digital video cameras (Sony High Definition Handycam® Camcorder; HDR-CX100) were placed on either side of the chamber. After 15 min of habituation, the rats were continuously videotaped for 30 min to obtain baseline grimace scores. The rats were given an IV dose of alcohol injection or saline and placed back in their home cage. Thirty minutes after IV injections, animals were returned to the Plexiglas chambers and videotaped continuously for 60 min.

Rodent face finder software (generously provided by Dr Jeffery Mogil) was used to scan each video frame for photographs with at least one eye and at least one ear detected, as described previously (Sotocinal et al. 2011). Photographs were acquired from digital videos of each rat at baseline (before injection), control (30–60 min after saline injection), and experimental conditions (30–60 min after alcohol injection). The captured images were copied to a folder, renamed, and randomized before blind scoring. We attempted to score four facial "action units" on a 0–2 scale (Sotocinal et al. 2011). These action units included scores of orbital tightening, ear changes, vibrissae retraction, and nose/cheek flattening. However, we could not evaluate changes in the ear position because our surgery to implant cannula affected ear position and the resolution of the images did not allow us to reliably assess vibrissae retraction or nose/cheek flattening. Therefore, we focused our analysis on scoring the orbital tightening action units. Ten photographs for each condition (baseline,

saline, alcohol) were obtained from each animal. Each photograph was relabeled for blind analysis. Photographs from all the animals and all experimental conditions were placed in a PowerPoint file in a random order. The photographs were scored by two investigators (Y.A. and R.M.) and orbital tightening scores were then averaged for each animal in each condition and then averaged across animals for each condition.

Statistical analysis

Condition place preference/avoidance paradigm. Two-way analysis of variance (ANOVA) was used. The independent variables were gender (male vs. female) and treatment (KCl vs. saline). Dunnett's test was used for *post hoc* analysis.

Mechanical hypersensitivity. Mechanical withdrawal thresholds were normalized to baseline values. One-way repeated measures ANOVA was use to compare changes in mechanical withdrawal thresholds over time (after alcohol/saline injection) to baseline values. Dunnett's test was used for *post hoc* analysis.

Orbital tightening scores. In animals treated with repeated applications of KCl, orbital tightening scores for all animals and all groups (baseline, saline, alcohol) were analyzed using one-way repeated measures ANOVA followed by Dunnett's multiple comparison test. In naive animals, orbital tightening scores were compared between the groups (baseline, alcohol) using the paired *t*-test. In all experiments, data were presented as mean ± SEM. A $p < 0.05$ was considered significant.

Results

The effect of meningeal KCl application on rats' place preference

We used the conditioned place preference/avoidance paradigm to test if repeated epidural administration of KCl is aversive to animals ($n = 17$ rats; 10 males and 7 females). Results from males (pre-conditioning: 60.1%, ±7.2; post-conditioning: 46.2%, ±13.4) and females (pre-conditioning: 59.6%, ±8.8; post-conditioning: 46.8%, ±18.2) were not significantly different ($F = 0.0001$; $p = 1.0$). Therefore, here and below, results from male and female animals were combined. As a group, during the pre-conditioning phase, animals spent 59.9% of the 15-min test period in the preferred chamber (Figure 2). Repeated application of KCl onto the meninges during the conditioning phase caused animals to develop an aversive response to the KCl-paired chamber during the post-conditioning phase and the time spent in the preferred chamber was significantly reduced to 46.3% ($F = 9.8$, $p = 0.004$; ANOVA; Figure 2). The result that animals avoided the KCl-paired chamber is consistent with previous studies showing that KCl administration to the meninges is noxious (Burstein et al. 1998; Fioravanti et al. 2011).

The effect of alcohol injection on mechanical withdrawal thresholds

On the left hindpaw (contralateral to cannula site), mechanical withdrawal thresholds assessed at baseline (before KCl applications) did not differ from thresholds assessed before alcohol injection or saline injection ($n = 14$, Figure 3A). However, when alcohol was injected, mechanical withdrawal thresholds were significantly reduced 60 min after injection and reached a maximum reduction between 90 and 120 min ($F = 11.504$, $p < 0.001$; ANOVA). Mechanical withdrawal thresholds returned to preinjection values 4 h after alcohol injection (Figure 3A). The same volume of saline had no effect on mechanical withdrawal thresholds ($F = 2.1$, $p = 0.5$; ANOVA; Figure 3A).

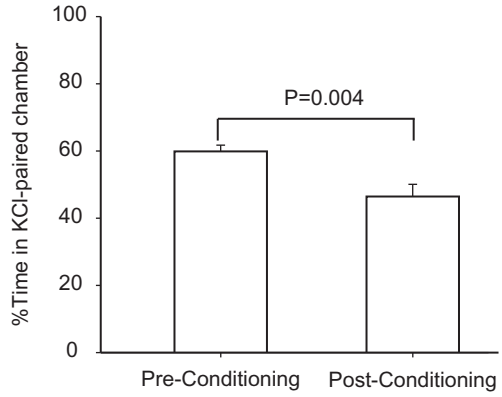

Figure 2. The effect of repeated applications of KCl to the meninges on conditioned place preference/avoidance. Animals spent significantly less time in the KCl-paired chamber ($p = 0.004$, $n = 17$).

We observed similar changes in the mechanical withdrawal thresholds of the right hindpaw (Figure 3B). Withdrawal thresholds were reduced significantly 60–120 min after alcohol injection ($F = 6.4$, $p < 0.001$; ANOVA) and returned to preinjection values within 4 h after alcohol injection. Saline injection had no effect on mechanical withdrawal thresholds of the right hindpaw ($F = 1.8$, $p = 0.1$; ANOVA). In naive animals, alcohol injection had no effect on mechanical withdrawal thresholds of either hindpaw ($n = 6$, left hindpaw: $F = 1.6$, $p = 0.2$; right hindpaw: $F = 1.7$, $p = 0.1$; ANOVA, Figures 3A and B).

The finding that alcohol, but not saline, injection reduced mechanical withdrawal thresholds in KCl-treated animals suggests that repeated applications of KCl render the animals prone to alcohol-induced reduction in withdrawal thresholds (extracephalic allodynia), a characteristic frequently observed in migraineurs (Jakubowski et al. 2005; Lipton and Bigal 2008; Olesen et al. 2009; Burstein et al. 2010).

The effect of alcohol injection on orbital tightening scores

Random, blind scoring of rat face photographs acquired using the Rat Face Finder Software revealed that orbital tightening scores increased significantly ($F = 12.2$, $p = 0.001$, $n = 7$; RM ANOVA) from baseline values of 0.1 ± 0.1 to 0.4 ± 0.3 AU after alcohol injection ($p < 0.05$, Dunnett's; Figure 4), but did not significantly change when saline was injected in the same animals (0.2 ± 0.1 AU; $p > 0.05$, Dunnett's; Figure 4). In naive animals ($n = 6$), alcohol injection had no effect on orbital tightening scores (before injection: 0.01 ± 0.03; after injection: 0.01 ± 0.03; $p = 0.9$; paired *t*-test; Figure 4E). These findings

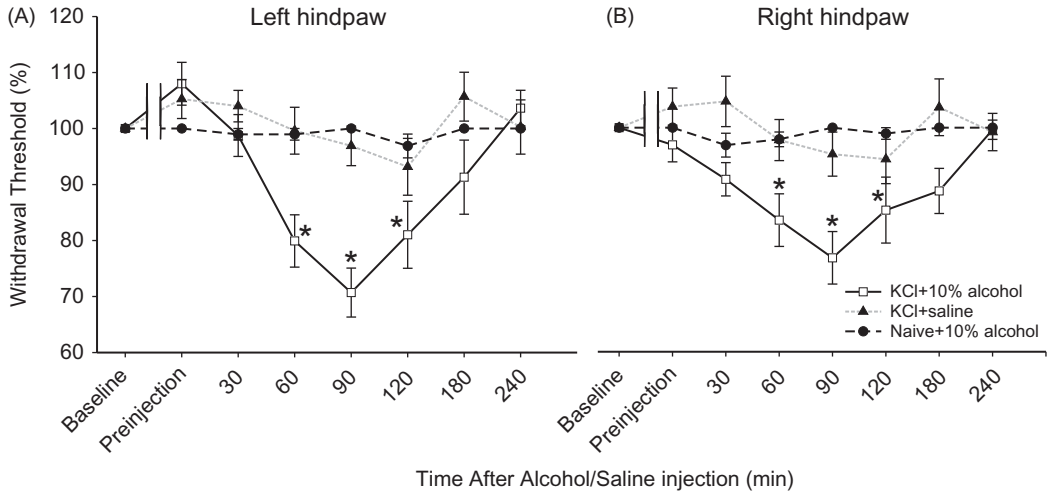

Figure 3. The effect of alcohol injection on hindpaw mechanical withdrawal thresholds in animals treated repeatedly with KCl. (A) In the left hindpaw (contralateral to implanted cannula) and the right hindpaw (B), alcohol injection ($n = 14$) resulted in significantly reduced mechanical withdrawal thresholds 60–120 min after injection. Saline injection had no effect on mechanical withdrawal thresholds in KCl-treated animals. Alcohol injection has no effect on mechanical withdrawal thresholds of naive animals ($n = 6$). Baseline = thresholds assayed in animals before cannula implantation.

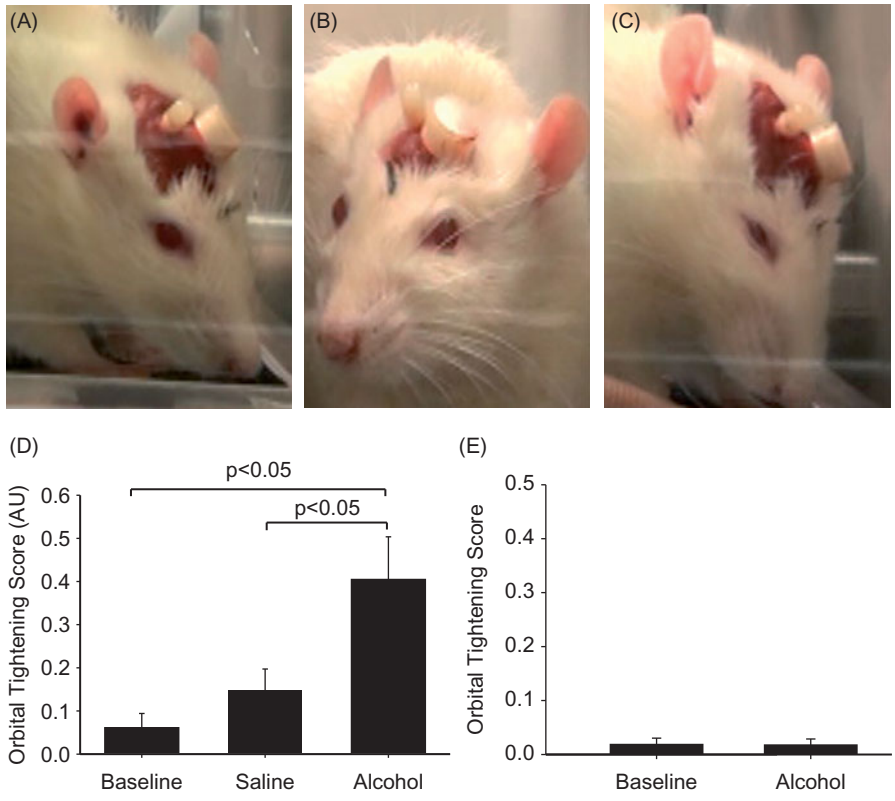

Figure 4. Assessment of orbital tightening in KCl-treated and naive animals. (A) Image captured from video recording of animal before injection and after 60–90 min after (B) saline or (C) alcohol injection. (D) These images where blindly scored for changes in orbital tightening ($n = 7$). KCl-treated animals exhibit significant orbital tightening when compared to baseline or saline injection, suggesting that these animals develop signs of ongoing pain due to alcohol injection. (E) There was no difference in orbital tightening scores before and after alcohol injections ($n = 6$, $p = 0.9$).

suggest that alcohol injection in KCl-treated animals triggers signs of ongoing pain.

Discussion

We hypothesized that repeated activation of meningeal afferents results in maladaptive plastic changes in the trigeminovascular system that cause animals to become sensitive to alcohol. To test this hypothesis, we applied KCl to the meninges to sensitize the trigeminovascular system, since peripheral and central sensitization of the trigeminovascular system is congruent with migraine in humans (Oshinsky and Gomonchareonsiri 2007; Edelmayer et al. 2012). Consistent with our hypothesis, repeated applications of KCl rendered the animals susceptible to alcohol-triggered extracephalic allodynia and signs of ongoing pain, key characteristics of migraine attacks in humans.

The results that KCl-treated animals, but not naive controls, developed both extracephalic allodynia and signs of ongoing pain suggest that repeated applications of KCl result in the sensitization of the trigeminovascular system and sensitization of central targets where trigeminal inputs and inputs from the hindpaws converge (e.g., the posterior thalamic nucleus) (Masri et al. 2009; Noseda et al. 2011).

In KCl-treated animals, the timeline of alcohol-induced behaviors resembles that of migraine triggered by alcohol ingestion. Extracephalic allodynia and signs of ongoing pain started to develop 30 min after alcohol injection. In humans, the interval between drinking alcohol and the development of migraine symptoms ranges from 30 min to 3 h (Raskin 1981; Littlewood et al. 1985). These behavioral changes recapitulate key clinical features of migraine headaches.

In humans, ingestion of a small amount of alcohol is enough to trigger a migraine attack (Panconesi et al. 2013). Therefore, we used an amount of alcohol (0.2 mg/kg) equivalent to that contained in a small glass of wine (125 ml) (Van den Bergh et al. 1987). This amount of alcohol did not produce behavioral changes in naive animals. Alcohol-triggered mechanical hypersensitivity in KCl-treated animals rather than hyposensitivity and the lack of alcohol-triggered behavioral changes in naive animals suggest that the orbital tightening is not due to alcohol toxicity. In a study investigating mechanisms of "hangover headaches" (Maxwell et al. 2010), a larger dose of alcohol (0.3 mg/kg) was administered to animals treated repeatedly with inflammatory soup to sensitize meningeal afferents. In these animals, alcohol resulted initially in decreased mechanical sensitivity in the face (hyposensitivity) after 1 h, a sign of alcohol intoxication. Four to six hours after alcohol administration, the animals developed cephalic mechanical hypersensitivity. The initial hypoalgesia and the delayed hypersensitivity are not consistent with our findings. However, the differences could be due to the higher dose of alcohol, the route of administration of alcohol (oral gavage), or the methods to sensitize trigeminovascular afferents.

The hallmark of migraine headaches is the presence of ongoing, debilitating, pain—an aspect of pain rarely studied in animal models of migraine. Therefore, we used methods to assess ongoing pain in our animals, including the use of conditioned place aversion, and the Face Grimace Scale test. However, although KCl applications chronically stimulated meningeal afferents so that the changes we observe could only be attributed to plastic changes in the trigeminal system, changes in rat face grimace could reflect pain at any part of the body that may not be limited to the cephalic region.

It is unknown why migraines are triggered by certain stimuli. However, it is speculated that frequent migraines induce changes in neuronal circuits that predispose migraineurs to hyperexcitability (Kelman 2007). A combination of pre-existing hyperexcitability and environmental stimuli can result in debilitating headaches. Several substances known to be included in alcoholic drinks are thought to be a trigger for headaches, including histamine, tyramine, phenylethylamin, sulphites, phenolic flavonoids, and acetate (Littlewood et al. 1985; Dahl et al. 1986; Jarisch and Wantke 1996; Nicolodi and Sicuteri 1999; Maxwell et al. 2010).

Ethanol, the active ingredient in alcohol, has also been cited as a trigger for migraine, especially at low doses. In acute low doses, alcohol may act as a vasodilator by increasing the release of nitric oxide, endothelial nitric oxide synthase, and CGRP (Gazzieri et al. 2006; Nicoletti et al. 2008). It may also cause the release of CGRP by activating the transient receptor potential vanilloid 1 receptors (TRPV1) (Nicoletti et al. 2008). The release of CGRP elicits neurogenic inflammation in the trigeminovascular system and may trigger migraines (Nicoletti et al. 2008).

Alcohol can also cause or facilitate the initiation of cortical spreading depression (the electrophysiological correlate of migraine aura) by contributing to the formation of reactive oxygen species or the release of nitric oxide and CGRP (Abadie-Guedes et al. 2008; Ayata 2010). In addition, acute consumption of some alcoholic drinks can cause serotonin release from platelets and central nervous system stores (Pattichis et al. 1995; Sandler et al. 1995). A sudden release in serotonin is also hypothesized as a trigger for migraines (Zhang et al. 2007).

Thus, it is apparent that there is no consensus regarding the etiology of migraine initiation with certain triggers. An animal model in which migraine-like signs can be triggered is an invaluable tool in preclinical research to study migraine pathophysiology and how it is initiated.

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Disclosure statement

The authors report no conflicts of interest.

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