Alcohol Induces Hangover Headache in Rats

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Objectives: We are currently studying the effects alcohol on the trigeminal neurovascular system which could provide new insights into the pathophysiology of headache induction using a trigger that is known to induce headaches in humans.

Background: A fundamental question in the pathophysiology of headache is "how is a headache induced?" The mechanism behind the induction of spontaneous headaches in migraineurs is unknown. Until recently, no animal models have been available to address this question. The experiments described below combines a model of recurrent headache with alcohol, a common trigger of headache in humans, to produce an inducible headache in a rat.

Methods: Our laboratory has developed a behavioral model of recurrent headache in rats, which uses repeated inflammatory activation of the trigeminal nociceptive pathway to simulate repeated headaches. The rats are implanted with a chronic canula above the dura for repeated infusions with an inflammatory soup while they are awake and freely moving. After 5-7 infusions, a stable change in trigeminal physiology is induced. There are four groups of rats in the preliminary studies described below. Two groups of rats received 8 saline infusions followed by an acute ingestion of either saline or alcohol on a day when they did not receive an infusion though the canula. Two additional groups of rats received 8 inflammatory soup infusions followed by either an acute ingestion of saline or alcohol. Sensory thresholds were measured using a Von Frey Pressure test.

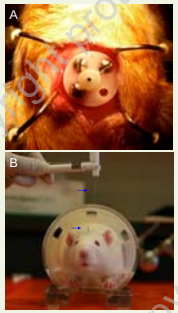


Figure 1 a and b: Canula, restrainer and Von Frey hair.

Von Frey Pressure (gm)	Response
10	Normal
8	Normal
6	Normal
4	Low
2	Hypersensitivity
1.4	Hypersensitivity
1	Hypersensitivity
0.6	Hypersensitivity

Table 1: Criteria for scoring sensory threshold

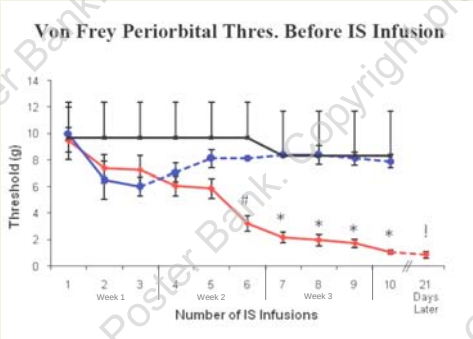


Figure 2: Morning periorbital thresholds for rats infused with saline(black), two IS infusions (blue) and repeated IS infusions (red). Note: decreased threshold in IS infused rats following repeated dura stimulations.

Results: In both groups that received saline infusions and the group that received inflammatory soup and saline gavage, there were no significant changes in sensory threshold following gavage compared to baseline state within each animal. The sensory threshold for the rats that received inflammatory soup and alcohol gavage changed significantly at both early (up to two hours) and late (four to six) timepoints following gavage. Interestingly, their sensory thresholds showed decreased sensitivity within two hours following alcohol ingestion suggesting alcohol may have a relaxation or analgesic effect on the rats. However, at 4 to 6 hours, the rats return to a threshold below their baseline level indicating that the alcohol induced a painful state.

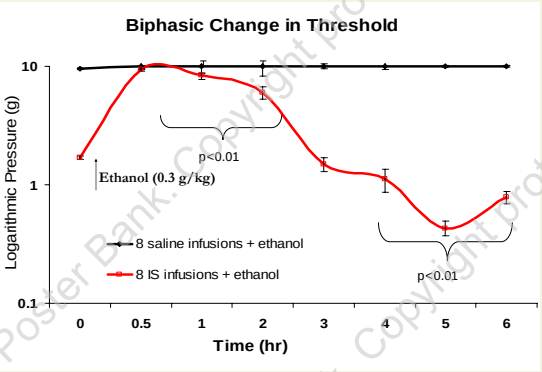


Figure 3: Alcohol induces analgesia within 2 hours followed by hypersensitivity at 4 to 6 hours only in IS infused rats. Red line represents 8 IS infusions followed by ethanol (0.3 g/kg) on non-infusion day (n=6). Black line represents 8 saline infusions followed by ethanol (0.3 g/kg) on non-infusion day (n=6).

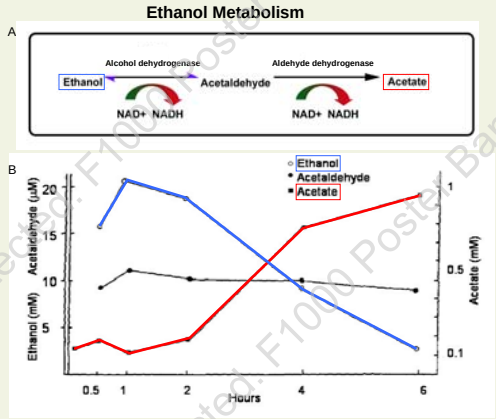


Figure 4 A: Ethanol metabolism cascade. Figure 4B: Human urine output of alcohol and metabolites over time. Adapted from Tuskamoto et al *Alcohol & Alcoholism, 1989 24(2):* 101-106. This figures provide rationale for acetate as a contributing factor in the hypersensitivity portion of ethanol's effect on pressure thresholds.

Oshinsky and Gomonchareonsiri 2007 Episodic Dural Stimulation in Awake Rats: A Model for Recurrent Headache. *Headache*;47:1026-1036

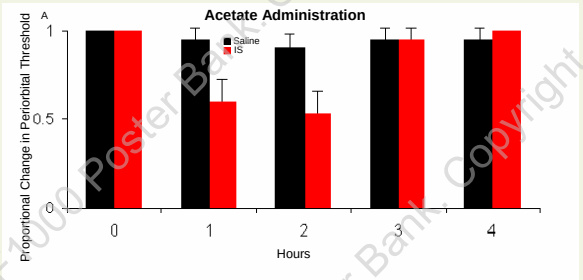
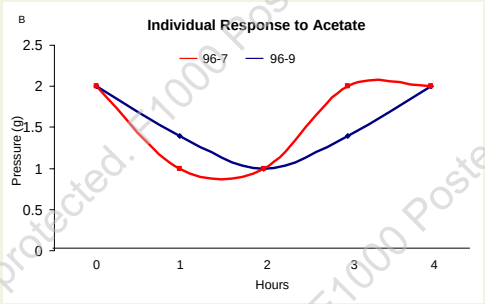


Figure 5 displays periorbital thresholds from overall (5A-above) and individual (5B-below) rats in response to acetate (20mg/kg i.p.) administration. Note: rats that received IS demonstrated decreased thresholds with acetate (N = 5 per group).



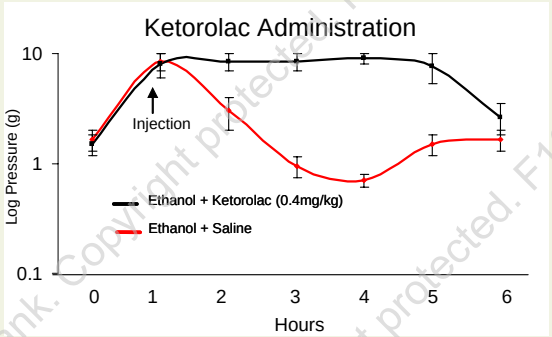


Figure 6: Ketorolac (0.4mg/kg i.p.) administered one hour after alcohol treatment inhibits alcohol-induced decrease in threshold.

Summary: Alcohol induces a biphasic change in trigeminal sensory thresholds in rats with a history of dural inflammation but not in rats who have no history of trigeminal pain. Initially alcohol causes analgesia as indicated by a decrease in pressure thresholds. Following this, rats become hypersensitive to light touch, which is probably due to the metabolite, acetate. These data demonstrate a model of alcohol induced headache that follows a time course similar to hangover headache in humans. This work provides a foundation for modeling the pathophysiology of headache, using a common trigger of headache in humans.

Study support: F31 AA017852 (CRM), R01 NS058695 (MLO), R21 NS061651 (MLO)