The (R)- isomer of isometheptene*, decreases trigeminal sensitivity in the Inflammatory Soup and Spontaneous Trigeminal Allodynia rat models.

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Abstract

Background:
Isometheptene, a racemic mixture of (R)- and (S)- enantiomers, is an active ingredient of the commonly known headache medication, Midrin. Although a previously assumed mechanism of action relied on the vascular hypothesis of migraine, the actual mechanism(s) remain elusive. Assessing the effect of each isomer individually in headache is essential in developing more efficacious treatment options for migraine patients. Two rat models of trigeminal pain which feature aspects of chronic migraine have been developed to allow for the testing of therapeutic compounds and investigation of the mechanisms behind migraine. The inflammatory soup (IS) model is developed by repeated dural infusion of an inflammatory soup 3x/wk for a month which results in chronic trigeminal sensitivty that outlasts the final infusion for months. The spontaneous trigeminal allodynia (STA) model is representative of primary headache since it is naturally expressed without experimental manipulation. Both these models experience similar symptoms to human migraine patients such as episodic or chronic trigeminal sensitivity, phonophobia, responsiveness to abortive and prophylactic headache treatments, and sensitivity to migraine triggers.

Objective:
The aim of this study was to test the effects of the (R)- and (S) isomers of isometheptene on trigeminal sensitivity in a the inflammtory soup and the spontaneous trigeminal allodynia rat models.

Methods:
The pharmacokinetics (PK) of racemic and (R)-isometheptene were studied in rats using isomer-specific LCMS. The effects of the (R)- and (S)- isometheptene on trigeminal sensitivity/allodynia in the IS and STA rats were analyzed. Animals for this study represent the 17th generation of an STA rat colony. Periorbital thresholds, as measured with von Frey filaments were obtained to determine trigeminal sensitivity prior to and 0.5 hr-, 1.5 hr-, 2.5 hr-, 3.5 hr-, and 24 hr-post treatment with (S)-isometheptene, (R)-isometheptene, or saline vehicle. All treatments were administered intraperitoneally.

Results:
Racemic and (R)-isometheptene had similar PK profiles (p.o.) with Tmax of 15-20 minutes and T(1/2) of 0.5 h and no isomeric conversion between (R)- and (S)- isometheptene.Treatment with 30 mg/kg of the (R)-isomer of isometheptene mucate significantly increased trigeminal thresholds at the 0.5 hr (2.3-fold), 1.5 hr (3.0-fold), 2.5 hr (2.9-fold), and 3.5 hr (1.7-fold) time points in IS rats (Fig. 3). Treatment with 30 mg/kg of the (R)-isomer of isometheptene mucate significantly increased trigeminal thresholds at the 0.5 hr (7.8-fold), 1.5 hr (4.3-fold), 2.5 hr (4.5-fold), 3.5 hr (8.5-fold), and 24 hr (8.2-fold) time points in STA rats (Fig. 6). In contrast, treatment with 30 mg/kg of the (S)- isomer, had no effect on trigeminal sensitivity in either the IS or STA models (Fig. 3 & 6). 1mg/kg of the (R) or (S) isomer had no effect on trigeminal sensitivity (Fig. 2 & 5).

Conclusions:
These data show (R)- isometheptene treatment relieved trigeminal sensitivity in the inflammatory soup and spontaneous trigeminal allodynia rat models, two models representative of the chronic nature of migraine. Additional dosing experiments are warranted to determine the dose response of this effect. These findings support development of the (R)-isomer of isometheptene as an abortive therapeutic for primary headache and other chronic pain indications.

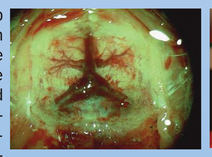
** (R)-isomethepetene is being investigated in the US for tension-type headache under a US IND and is not approved for any indication.*

Introduction

Midrin, containing Isometheptene Mucate (65 mg); Dichloralphenazone (100 mg) and Acetaminophen (325 mg), is indicated for relief of migraine headache. It was initially believed that isometheptene's vasoactive effects were responsible for Midrin's efficiacy in migraine. Isometheptene, however, is a racemic mixture of (R)- and (S)- enantiomers; each with its own very distinct receptor-interaction profile. The (R)- isomer has high specificity as an agonist for imidazoline receptor type 1 (I1) while the (S)- isomer has no affinity for this receptor. I1 receptor knock-out mice feature reduced pain phenotypes, suggesting that this receptor may be involved in pain and that the (R)- isomer could be the effective component to isometheptene's role in migraine headache treatment via this receptor (Zhang, 2013).

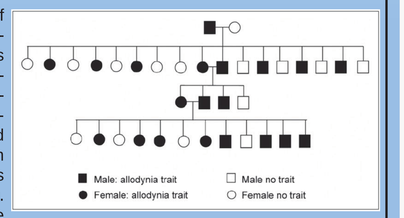
Chronic Migraine Model

Rats were fitted with a cannula for inflammatory soup infusions (Bradykinin, PGE2, 5-HT, Histamine). Von Frey testing was done in a plastic tube restraint in the periorbital region of the rat above the rostral part of the eye. Threshold was noted when rats quickly retracted their head away from the bending von Frey monofilament or performed a long brush of its face with the ipsilateral paw. Infusions were performed 3x/wk to simulate episodic activation of dural nociceptors in chronic migraine (Fig. 1) (Oshinsky, 2007).



Spontaneous Trigeminal Allodynia Model

Most animal headache models require manipulation of the animal, often with a stimulus to activate dural nociceptors or the trigeminal nerve. Using behavioral methods of monitoring trigeminal pain in rats, our group discovered a rat with spontaneous episodic trigeminal allodynia. Subsequent mating showed that the trait is inherited in 40-50% of offspring from affected animals crossed to unaffected animals, and in ~60-70% of offspring from crosses with 2 affected animals. A stable colony has been established through 18 generations of inbreeding. These rats exhibit episodic threshold decreases that are responsive to treatment by NSAIDS, triptans, and DHE. They also experience phonophobia (Oshinsky, 2012).



Results - Inflammatory Soup Model

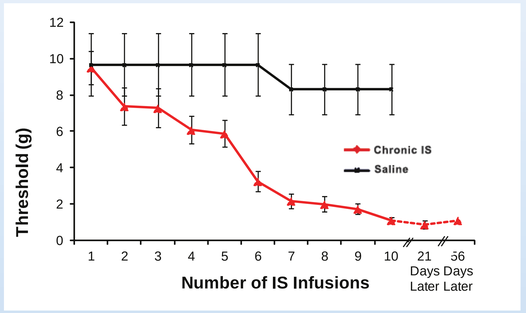


Figure 1: Trigeminal sensitivity in the inflammatory soup model.
To assess trigeminal allodynia, periorbital Von Frey Minofilament thresholds were measured throughout the treatment period in rats receiving infusions of saline (n=10) or IS (n=10) 3 days/week. Rats receiving infusions of IS "transitioned" to a more sensitive state, as seen as a decrease in their periorbital thresholds, whereas rats receiving saline infusions did not transition to a more sensitive state. Rats that have "transitioned" to chronic periorbital sensitivity have thresholds of < 2.0g. Naive or non-transitioned rats do not respond to any pressure less than 8-10g.

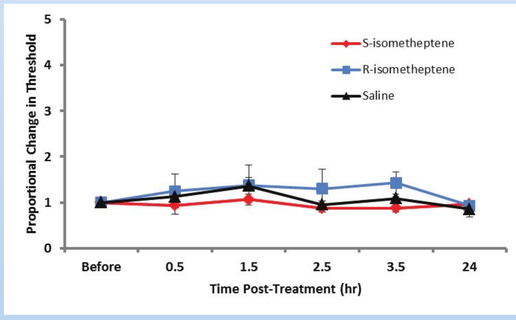


Figure 2: Effects of 1mg/kg of R- & S-enantiomers of isometheptene on trigeminal sensitivity in the inflammatory soup model.

No significant changes in trigeminal sensitivity were seen when IS rats were treated with 1mg/kg R- or S- isometheptene (i.p.) (n=8 rats/group).

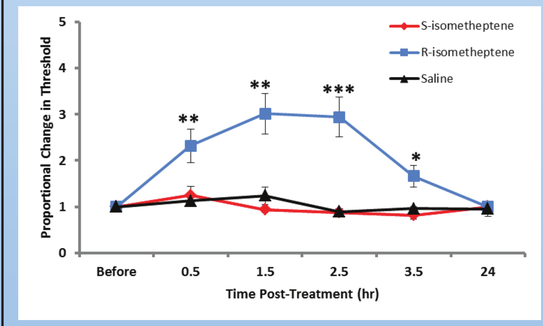


Figure 3: Effects of 30mg/kg of R- & S-enantiomers of isometheptene on trigeminal sensitivity in the inflammatory soup model.

30mg/kg of R-isometheptene decreased trigeminal sensitivity while 30mg/kg of S-isometheptene had no effect on sensory thresholds. Rats receiving saline treatment had no change in sensory thresholds over the course of the experimental timeline. (n=8 rats/group, *P<0.05, **P<0.01, ***P<0.001).

Results - STA Model

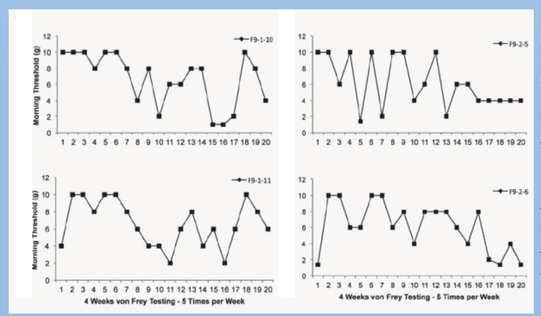


Figure 4: Trigeminal Sensitivity in the Spontaneous Trigeminal Allodynia rat model.

Trigeminal threshold tracking for four individual rats in the 9th generation. The heterogeneic pattern of periorbital von Frey threshold changes are seen in these rat.Tests were done 5 times per week for 4 weeks. Thresholds were obtained in the morning, within the 3 hours after the lights were turned on.

Results - STA Model

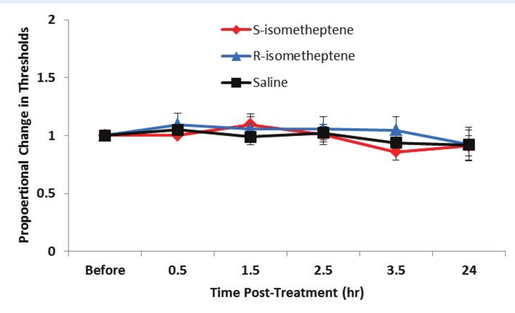


Figure 5: Effects of 1mg/kg of R- & S- enantiomers of isometheptene on trigeminal sensitivity in the STA model.

No significant changes in trigeminal sensitivity was seen when STA rats were treated with 1mg/kg R- or S- isometheptene. (n=8 rats/group).

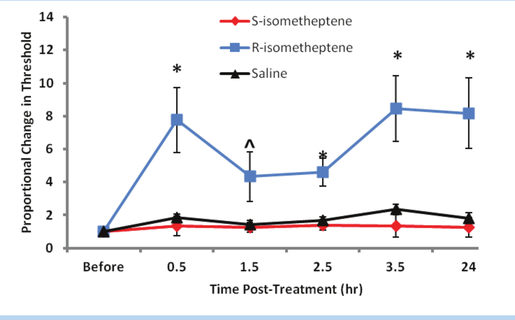


Figure 6: Effects of 30mg/kg of R- & S- Enantiomers of isometheptene on trigeminal sensitivity in the STA model.

30mg/kg of R-isometheptene decreased trigeminal sensitivity while 30mg/kg of S-isometheptene had no effect on sensory thresholds. Rats receiving saline treatment had no change in sensory thresholds over the course of the experimental timeline. (n=8 rats/group, *P<0.01, ^P<0.05).

Summary

-Treatment with 30mg/kg of (R) isomer of isometheptene reduces trigeminal sensitivity in both the inflammatory soup and spontaneous trigeminal allodynia rat models. 1mg/kg is not sufficient to produce these changes.

-The (S) isomer of isometheptene has no impact on trigeminal sensitivity.

-These results suggest that isometheptene's effect in headache treatment is due (R) isomer -pecific downstream mechanisms.

Citations

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Poster Citation

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