Developing a “Migraneous” Rat Model to Evaluate the Efficacy and Mechanisms of OMT on Migraine Relief

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Methods

- Migraine
  - Recurrent unilateral throbbing cephalic pain
  - Associated with hypersensitivity to a variety of external stimuli, e.g. light, smell, and sound
  - Neck pain is a common comorbidity

- Sensitization and activation of the trigeminocervical complex

- A novel rodent model of migraine
  - Durham group sensitized rats with CFA and then exposed them to California Bay Leaves
  - We used CFA + Umbellulone
  - New behavior endpoint – spontaneous running-wheel activities

- Clinically, OMT increase migraneurs’ quality of life scores
  - Weak clinical trial efficacy
  - No mechanistic studies

- Our goal is to demonstrate the pathophysiologic underpinnings of OMT utilizing an established model of migraine pathology in rodents.

Umbellularia Californica - “headache tree”
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Introduction

Methods

• Female Sprague Dawley Rats
• “Double-hit” strategy – Priming with Complete Freund Adjuvant (CFA, 10 μL/injection, 5 injections/side) to the trapezius muscle
• Trigger with Umbellulone (50 mM/50 μL), the major volatile molecule of the California Bay Leaf, for 30 minutes at 2% O2
• OMT: 1 min articulatory techniques, and 1 min soft tissue techniques
• Behaviors were measured for 5 hours

Cephalic Allodynia

Voluntary Wheel-Running

Group A

Day ~2-0

Acclimation

Day 1

Test VF BL, CFA Inj.

Day 2

OMT/SHAM

Day 8

t= 0 h

OMT/SHAM Treatment

Test VF hourly

Umbellulone Inhalation

Group B

Day ~14-0

Running Wheel Training

Day 1

CFA Inj.

Day 2

OMT/SHAM

Running Wheel

Day 4

OMT/SHAM Treatment

Running Wheel

Day 8

t= 0 h

Umbellulone Inhalation

OMT/SHAM

Running Wheel

t= 1.5 h

Running Wheel

Von Frey Chambers

Umbellulone Inhalation Chamber

Inhalation Chamber
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Introduction

Cephalic Alldynia

Effect of OMT on Umbellulone-induced alldynia in CFA-primed SD rats.

Periorbital tactile threshold was assessed for baseline and hourly for 5 hours after Umbellulone or vehicle exposure with calibrated von Frey filaments (cut off = 8g).

A. Umbellulone significantly lowered tactile threshold at 2 and 3 h post-dose in CFA primed rats. Saline-primed rats maintained normal threshold (n=5/group). P<0.05 compared to pre-umbellulone baseline to post-CFA on Day 8.

B. OMT significantly diminished the development of periorbital allodynia induced by Umbellulone in CFA-primed rats. OMT was applied in some rats for 2 min under 2% isoflurane by a D.O. OMT was given at 3 times (D2, D4, D8 post-UMB). N=8/group. P<0.05 compared to corresponding control group at the same time point.

Voluntary Wheel-Running Activity

Effect of Umbellulone inhalation on wheel-running activity in CFA-primed rats across 4 day awake models, 8 day anesthetized models, and 8 day awake models.

C. & D. Umbellulone reduced voluntary running-wheel activities in CFA-primed rats. The difference between treatment and baseline indicated UMB treated rats experienced a decrease in spontaneous activity compared to vehicle groups at 1 and 2h post dose. N=3-4/group.

E, F & G. OMT showed a trend of reducing the impact of umbellulone. Prolonged isoflurane exposure has shown strong confounding effects to this behavior.
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- The Primary goal of our study is to \textbf{increase the evidence base} by which OMT can be used to treat migraines by examining its pathophysiology in a rodent model.
- At this time, we have modeled OMT’s success in reducing \textbf{cephalic allodynia} in migraneous rats.
- We continue to make \textbf{step-wise adjustments} to our voluntary running-wheel model from performing OMT in anesthetized to awake animals and then shortening the time course. We hypothesize that, as in human, the rats may be experiencing soreness post-treatment. To mitigate this we plan to change the time course of the OMT/sham treatment themselves as if patient were coming in for treatment during the prodrome period of a migraine.
- \textbf{Next steps} include gathering blood serum CGRP ELISA data and examining the trigeminal ganglia and trigeminal nucleus caudalis utilizing immunohistochemistry.
References


