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

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Introduction

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 Leaf extract
- We used CFA + Umbellulone (TRPA1 agonist)
- New behavior endpoint – spontaneous running-wheel activities

Clinically, OMT increase migraineurs’ 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.
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Methods

Introduction

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

Results

Discussion

Cephalic Allodynia

- Umbellulone Inhalation Chamber
- Voluntary Wheel-Running

Group A

- Day 1: CFA Inj.
- Day 2: OMT/SHAM Running Wheel

Group B

- Day 1: CFA Inj.
- Day 2: OMT/SHAM Running Wheel

Running Wheel Setup
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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 hour after Umbellulone or vehicle exposure with calibrated von Frey filaments (cutoff = 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 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.
The Primary goal of our study is to 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 cephalic allodynia in migraneous rats.

We continue to make 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.

Next steps include gathering blood serum CGRP ELISA data and examining the trigeminal ganglia and trigeminal nucleus caudalis utilizing immunohistochemistry.
References


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