

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

NEW YORK INSTITUTE  
OF TECHNOLOGY

College of Osteopathic  
Medicine | Arkansas

Katherine Byrd OMS III<sup>1</sup>, Caroline Gregory OMS II<sup>1</sup>, Krishna Sharma<sup>3</sup>, Jennifer Xie PhD<sup>1</sup>, Regina Fleming DO<sup>2</sup>

<sup>1</sup>Department of Basic Science, <sup>2</sup>Department of Osteopathic Manipulative Medicine, New York Institute of Technology College of Osteopathic Medicine - Arkansas, Jonesboro, Arkansas; <sup>3</sup>Biological Science and Arkansas Bioscience Institute, Arkansas State University, Jonesboro, Arkansas

Introduction

Methods

Results

Discussion

- 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.



Umbellularia Californica -  
“headache tree”



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

Katherine Byrd OMS III<sup>1</sup>, Caroline Gregory OMS II<sup>1</sup>, Krishna Sharma<sup>3</sup>, Jennifer Xie PhD<sup>1</sup>, Regina Fleming DO<sup>2</sup>

<sup>1</sup>Department of Basic Science, <sup>2</sup>Department of Osteopathic Manipulative Medicine, New York Institute of Technology College of Osteopathic Medicine - Arkansas, Jonesboro, Arkansas; <sup>3</sup>Biological Science and Arkansas Bioscience Institute, Arkansas State University, Jonesboro, Arkansas

Introduction

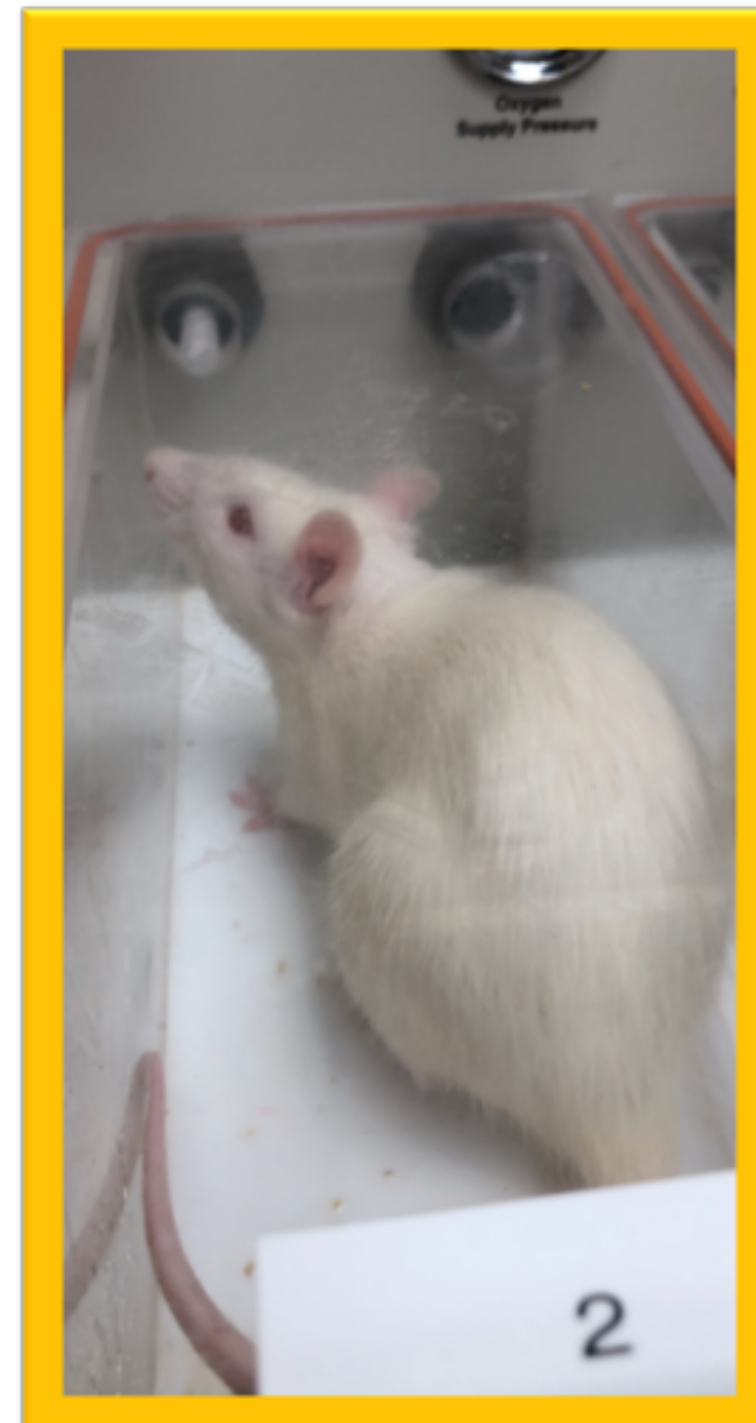
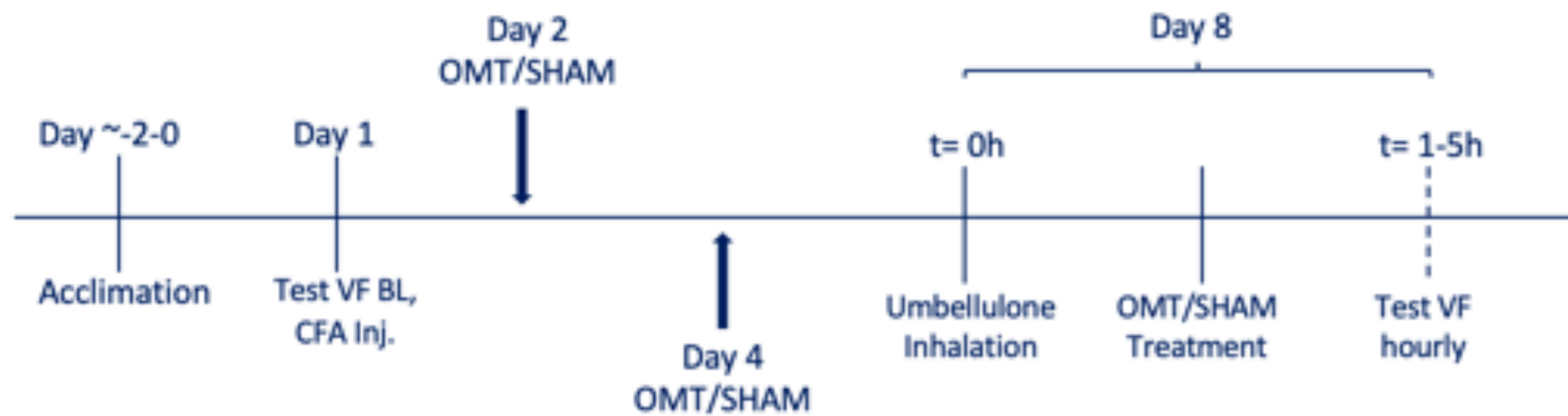
Methods

Results

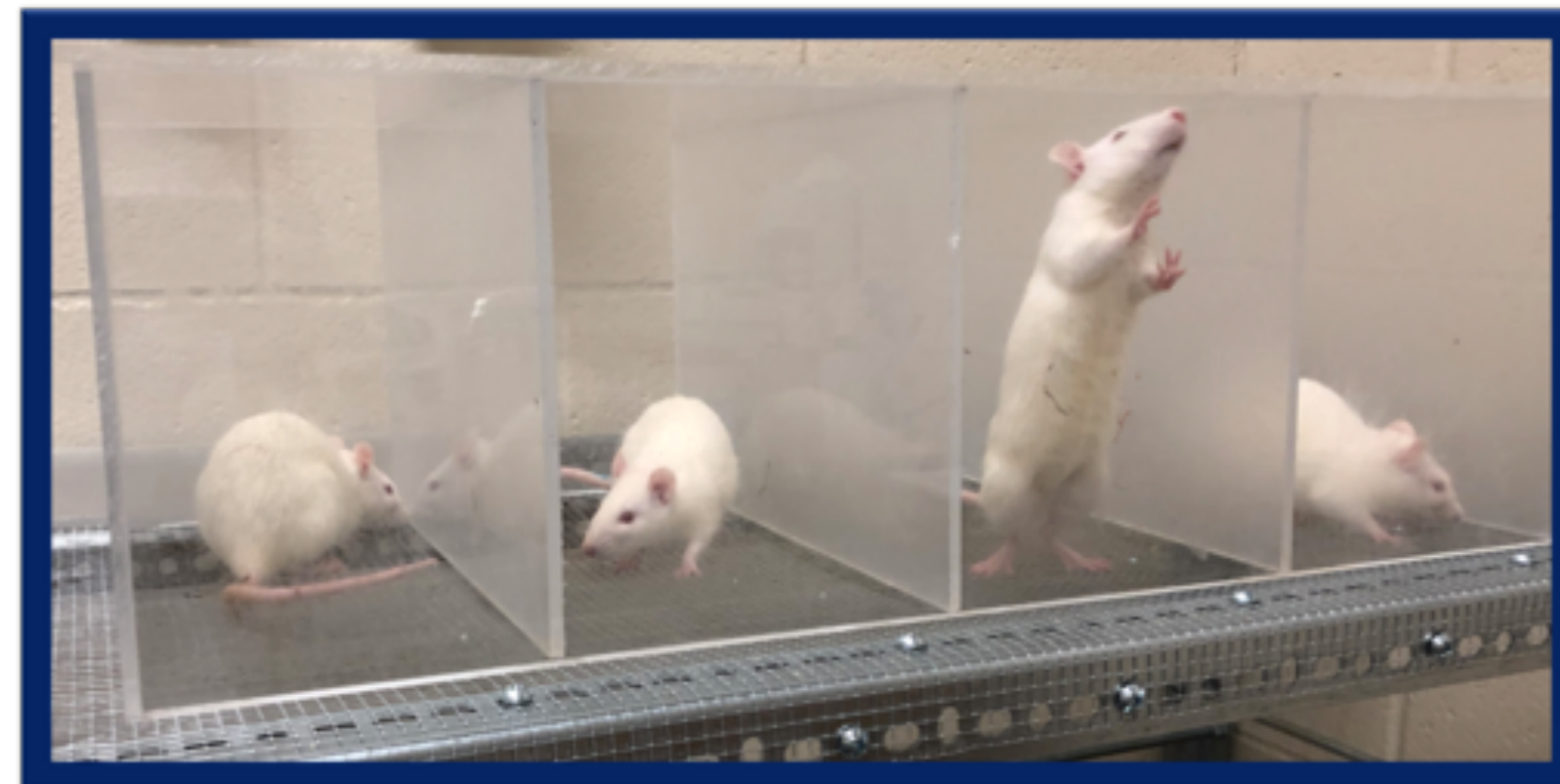
Discussion

- **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 articular techniques**
- **Behaviors were measured for 5 hours**

## Cephalic Allodynia



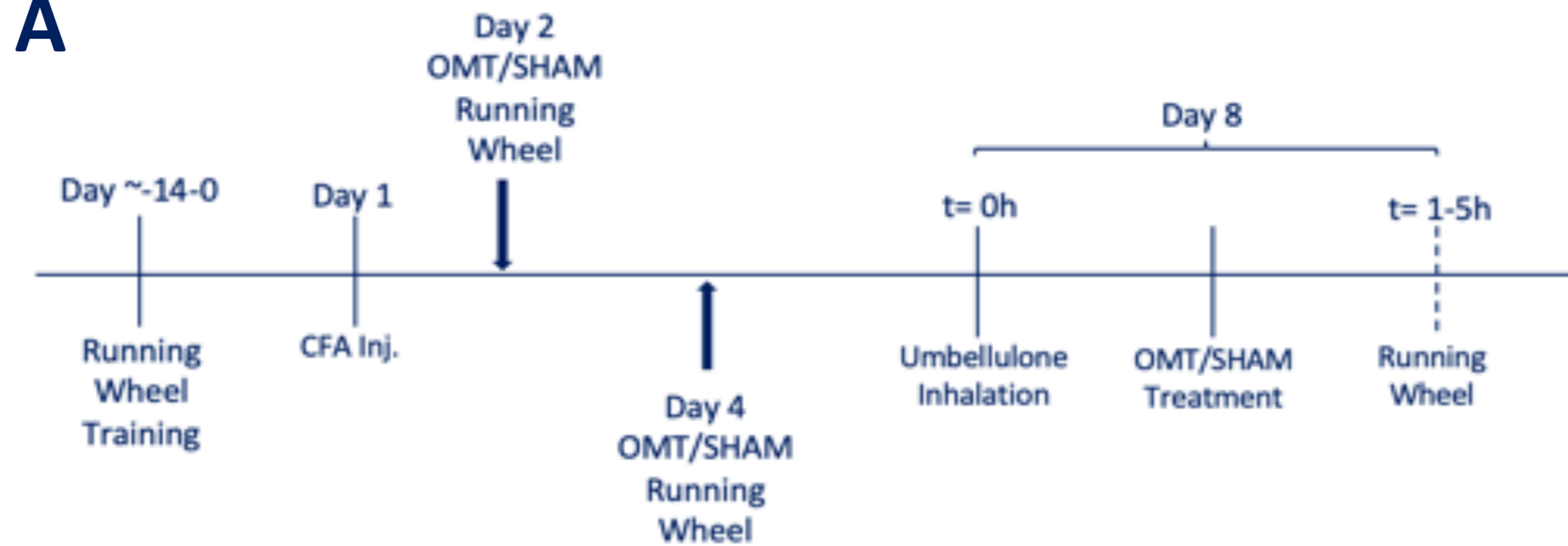
Umbellulone Inhalation Chamber



Von Frey Chambers

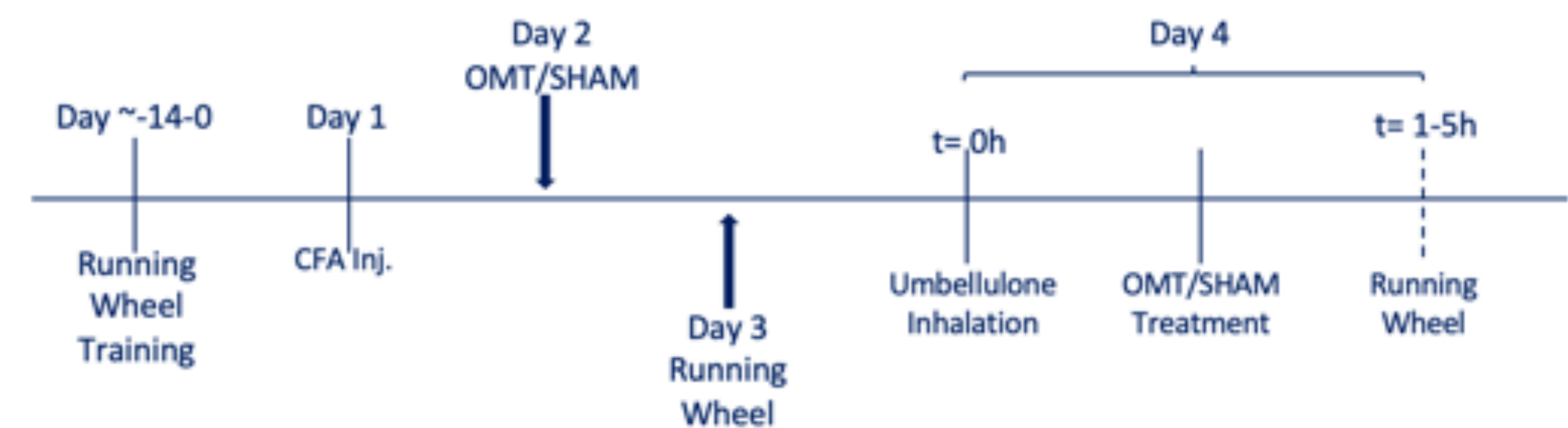
## Voluntary Wheel-Running

### Group A



Running Wheel Setup

### Group B



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

Katherine Byrd OMS III<sup>1</sup>, Caroline Gregory OMS II<sup>1</sup>, Krishna Sharma<sup>3</sup>, Jennifer Xie PhD<sup>1</sup>, Regina Fleming DO<sup>2</sup>

<sup>1</sup>Department of Basic Science, <sup>2</sup>Department of Osteopathic Manipulative Medicine, New York Institute of Technology College of Osteopathic Medicine - Arkansas, Jonesboro, Arkansas; <sup>3</sup>Biological Science and Arkansas Bioscience Institute, Arkansas State University, Jonesboro, Arkansas

Introduction

Methods

Results

Discussion

## Cephalic Allodynia

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

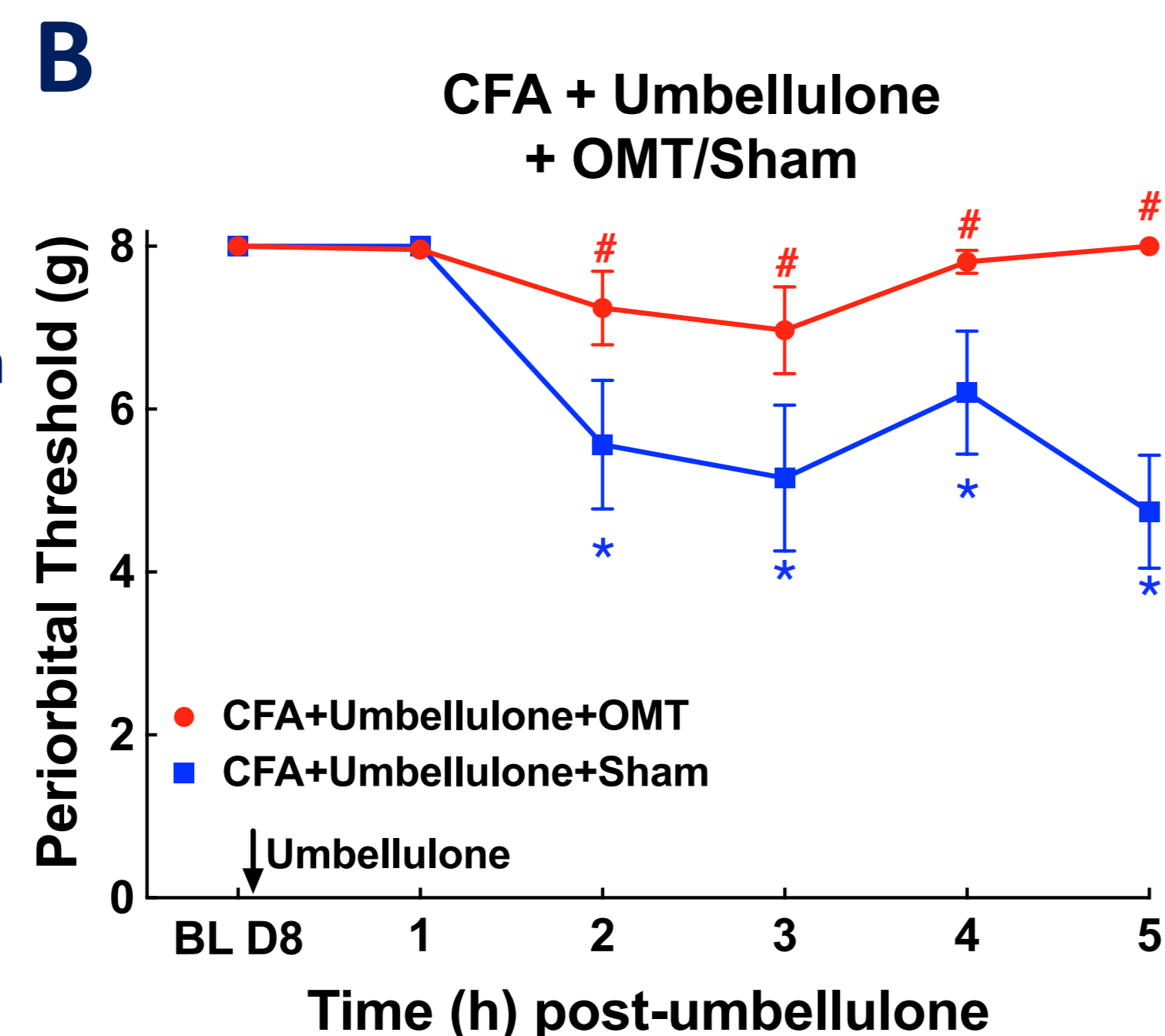
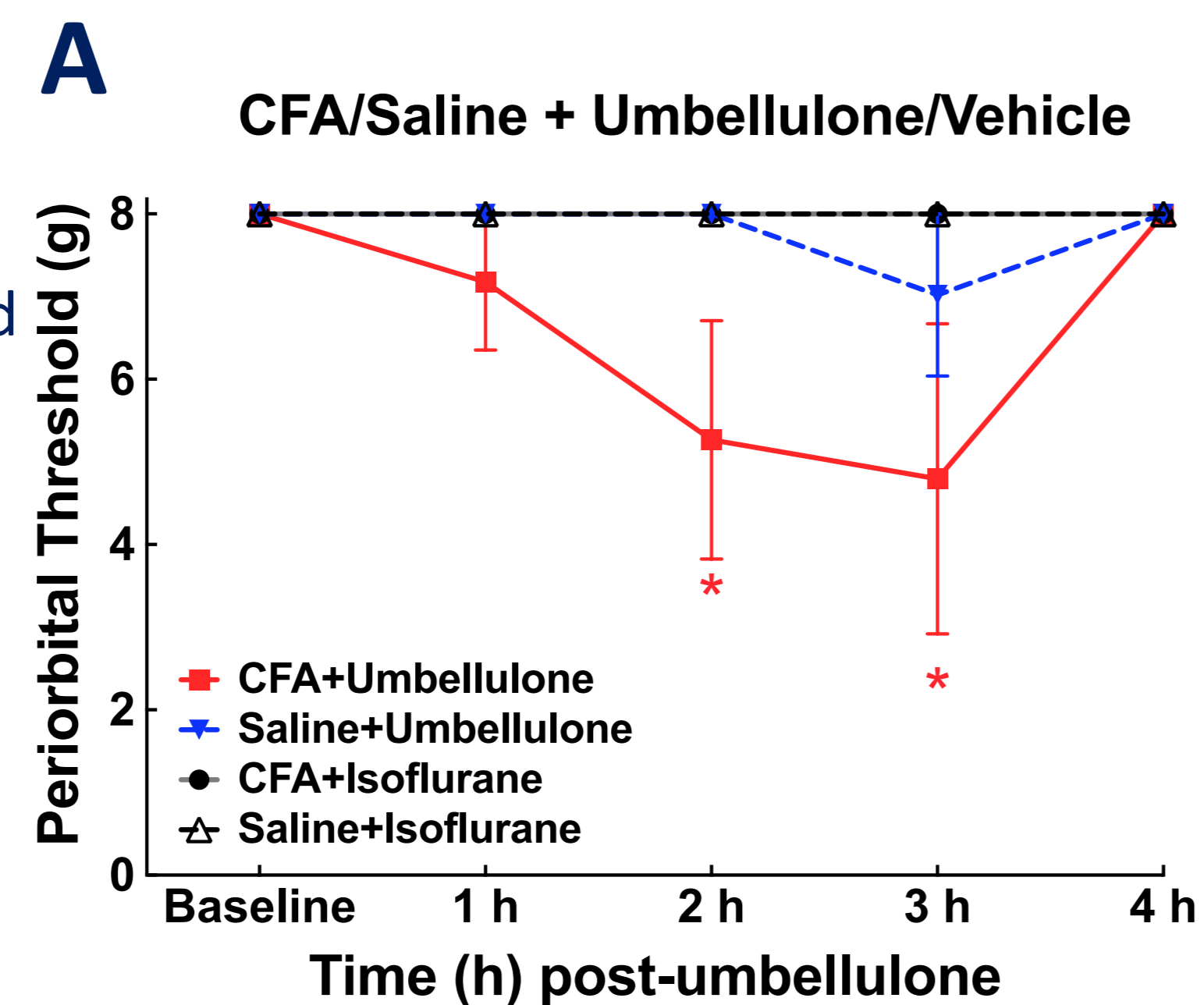
Periorbital tactile threshold was assessed for baseline and hourly for 5 hour after Umbellulone or vehicle exposure with calibrated von Frey filaments (cutoff = 8g).

#### A. Umbellulone significantly lowered tactile threshold at 2 and 3 h post-dose in CFA primed rats.

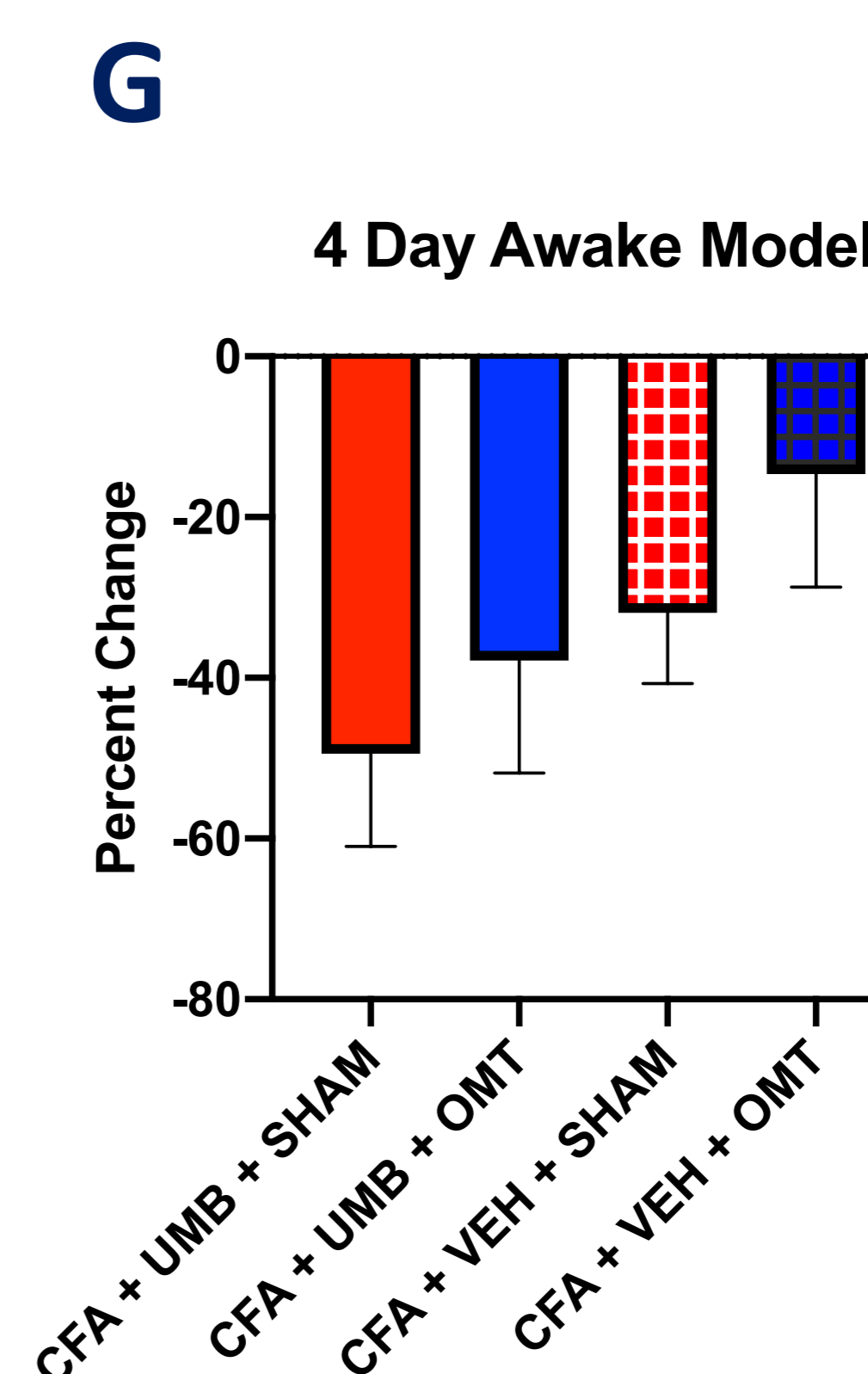
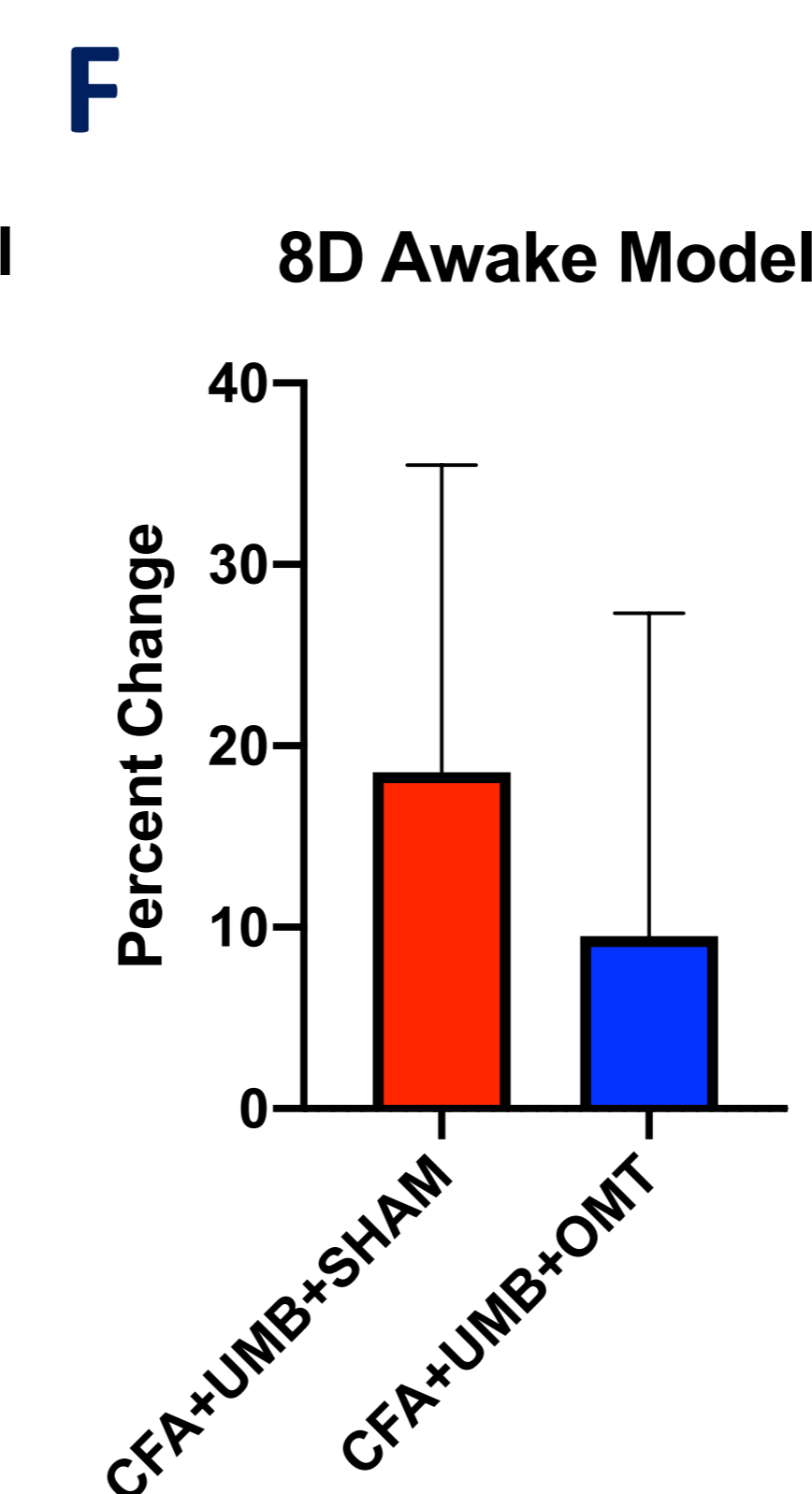
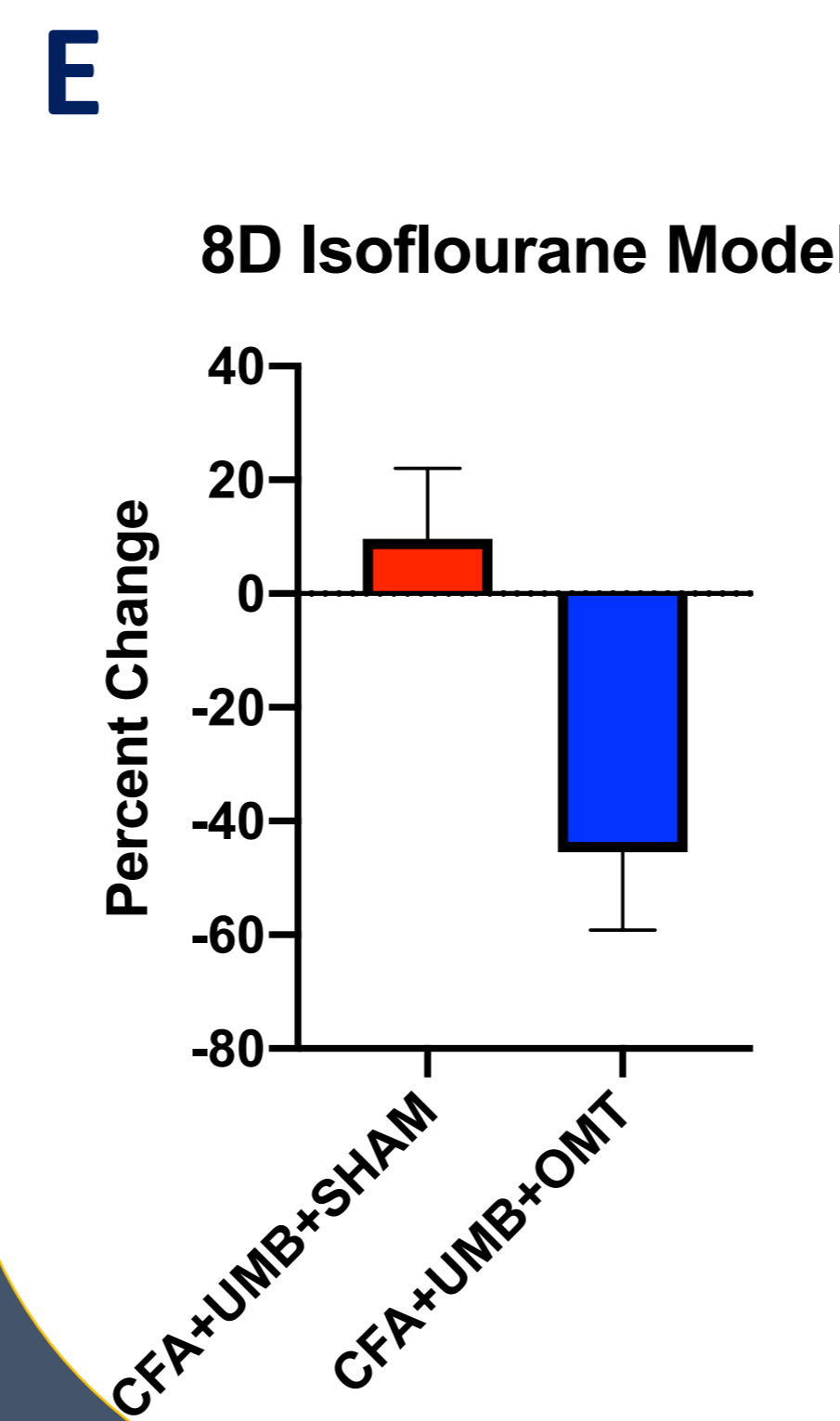
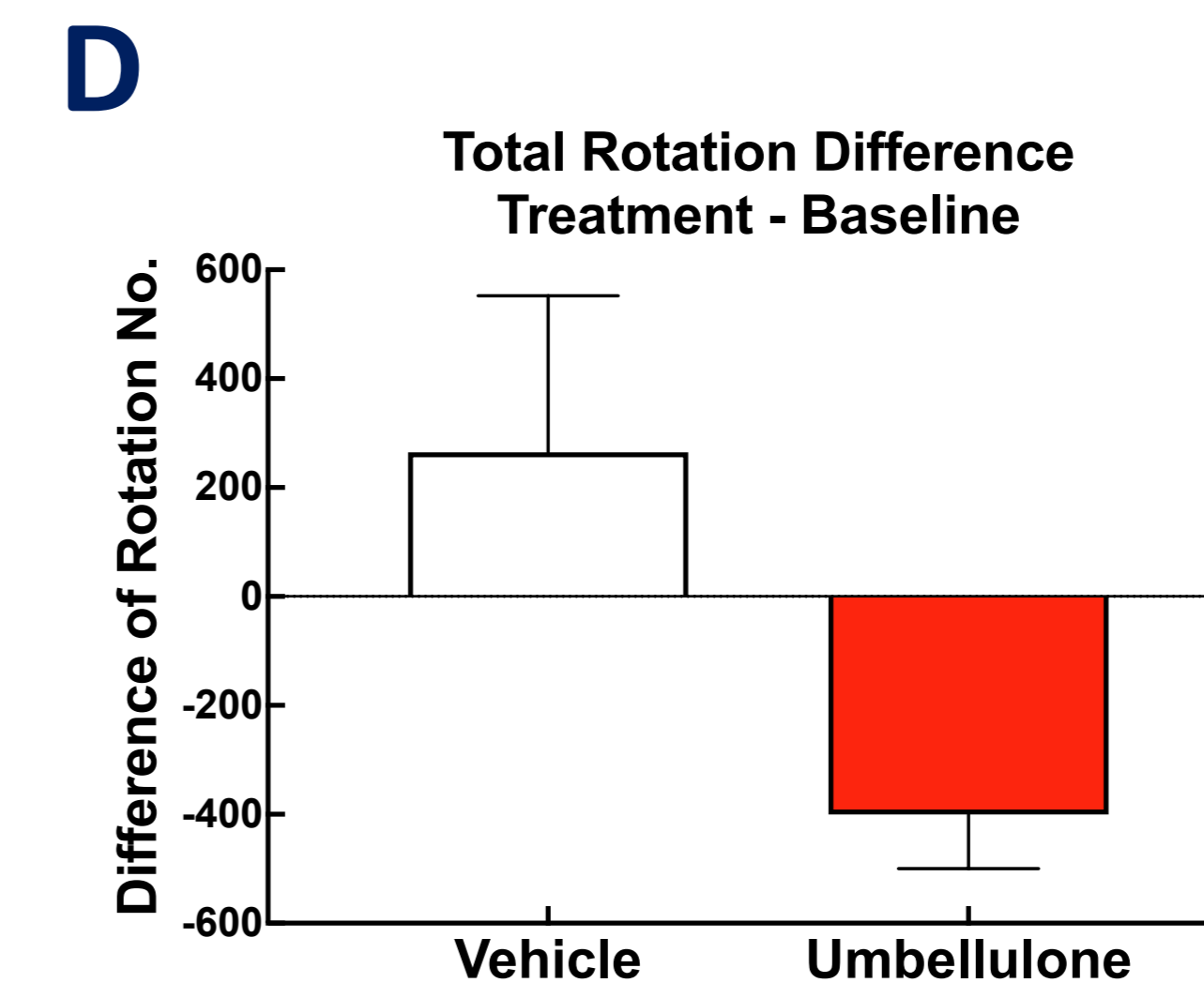
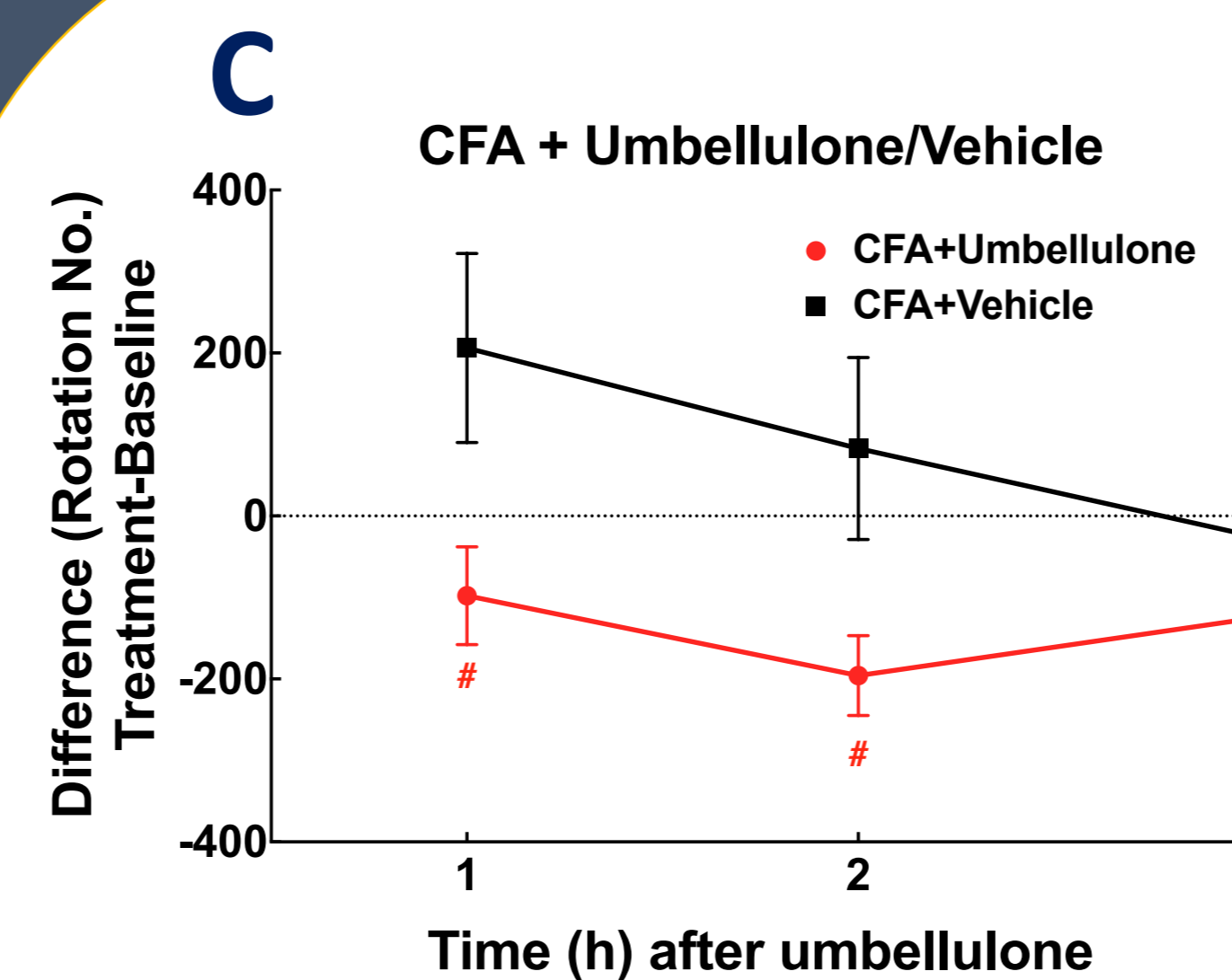
Saline-primed rats maintained normal threshold (n=5/group). P<0.05 compared to pre-umbellulone baseline to post-CFA on Day 8.

#### 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% isoflourane 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 isoflourane exposure has shown strong confounding effects to this behavior.

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

Katherine Byrd OMS III<sup>1</sup>, Caroline Gregory OMS II<sup>1</sup>, Krishna Sharma<sup>3</sup>, Jennifer Xie PhD<sup>1</sup>, Regina Fleming DO<sup>2</sup>

<sup>1</sup>Department of Basic Science, <sup>2</sup>Department of Osteopathic Manipulative Medicine, New York Institute of Technology College of Osteopathic Medicine - Arkansas, Jonesboro, Arkansas; <sup>3</sup>Biological Science and Arkansas Bioscience Institute, Arkansas State University, Jonesboro, Arkansas

Introduction

Methods

Results

Discussions

- 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.



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

Katherine Byrd OMS III<sup>1</sup>, Caroline Gregory OMS II<sup>1</sup>, Krishna Sharma<sup>3</sup>, Jennifer Xie PhD<sup>1</sup>, Regina Fleming DO<sup>2</sup>

<sup>1</sup>Department of Basic Science, <sup>2</sup>Department of Osteopathic Manipulative Medicine, New York Institute of Technology College of Osteopathic Medicine - Arkansas, Jonesboro, Arkansas; <sup>3</sup>Biological Science and Arkansas Bioscience Institute, Arkansas State University, Jonesboro, Arkansas

## Acknowledgements

- Lab Members
- Funding Agency
  - Research Catalyst Grant (NYITCOM)



## References

1. Goadsby, P. J. Pathophysiology of migraine. *Neurol Clin* 27, 335-360, doi:S0733- 8619(08)00171-0 [pii] 10.1016/j.ncl.2008.11.012 (2009).
2. Hawkins, J. L., Cornelison, L. E., Blankenship, B. A. & Durham, P. L. Vagus nerve stimulation inhibits trigeminal nociception in a rodent model of episodic migraine. *Pain Reports* in press (2017).
3. Espi-Lopez, G. V. et al. Effect of Soft Tissue Techniques on Headache Impact, Disability, and Quality of Life in Migraine Sufferers: A Pilot Study. *J Altern Complement Med* 24, 1099-1107, doi:10.1089/acm.2018.0048 (2018).
4. Biondi, D. M. Cervicogenic headache: a review of diagnostic and treatment strategies. *J Am Osteopath Assoc* 105, 16S-22S (2005).
5. Nassini, R. et al. The 'headache tree' via umbellulone and TRPA1 activates the trigeminovascular system. *Brain* 135, 376-390, doi:10.1093/brain/awr272 (2012).
6. Blau, J. N. & MacGregor, E. A. Migraine and the neck. *Headache* 34, 88-90 (1994).
7. Image 1: <https://www.nwf.org/Educational-Resources/Wildlife-Guide/Plants-and-Fungi/California-Bay-Laurel.aspx>