Animal Models of Headache

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Disclosures
Learning Objectives

Discuss some of the advantages and limitations of animal models to study headache

Describe 3 different animal models of migraine and other headaches

Explain the importance of clinically-relevant outcome measurements when using animal models
Outline

Basic aspects of animal models of headache

Overview of established animal models of migraine

Animal models of other headaches

Application of animal models to investigate the role of obesity in migraine
Why are animal models important?

Understand disease & Develop treatments
Advantages of Animal Models of Headaches

Allow mechanistic studies of headache pathophysiology

Increasing advances in genetic manipulation and other techniques

Contributions of environment and genetics can be controlled (?)

Provide proof-of-concept evidence before testing drugs in humans
Limitation of Animal Models of Headaches

Heterogeneous disorders

Limited understanding of pathophysiology & genetics

Species differences

Low throughput

Cannot recapitulate the complete disorder

...YET
Important Considerations

Availability
Generalizability
Price
Size
Sex
Question
Established Animal Models of Migraine

**Dura stimulation**
- Electrical
- Mechanical
- Chemical

(Burstein et al., J Neurophys 1998)
(Oshinsky et al., Headache 2007)

**Cortical spreading depression**
- KCl
- Mechanical
- Electrical

(Ayata, Cephalalgia 2013)

**Pharmacological provocation**
- NTG
- CGRP
- PACAP38

(Bates et al, Cephalalgia 2009)
(Kaiser et al, J Neurosci 2012)
(Akerman et al, Sci Transl Med 2015)

**Genetic models**
- Familial Hemiplegic Migraine
- Casein Kinase 1 delta
- CGRP sensitized mice

(Chanda et al, Pain 2013)
(Brennan et al, Sci Transl Med 2013)
(Recober et al, J Neurosci 2009)
Beyond Migraine

- Trigeminal neuralgia
- Cluster headache
- Post-traumatic headache
- Medication overuse headache
Animal models to study trigeminal neuralgia

OUTCOMES:
Feeding behavior
Tactile allodynia
Air puff allodynia
Histological changes

(Kim et al, Neuron 2014)
(Yeomans, Methods in Mol Biol, 2012)
Animal model to study cluster headache

(Akerman et al., Brain 2012)
Animal models to study post-traumatic headache

Controlled Cortical Impact (CCI)

Fluid Percussion Injury (FPI)

Blast TBI

Feeney Weight-Drop

Marmarou Weight-Drop

Trigeminal Pain Molecules, Allodynia, and Photosensitivity Are Pharmacologically and Genetically Modulated in a Model of Traumatic Brain Injury

Brittany V. Dautolo, Ashley Tyburski, Shannon W. Clark, and Melanie B. Elliott

(Xiong et al, Nat Rev Neurosci 2013)
(Daiutolo et al, J Neurotraum 2016)
Animal model to study medication overuse headache

SUSTAINED EXPOSURE TO TRIPTANS

(De Felice et al, Ann Neurol 2010)
Does obesity modulate migraine pathophysiology?

Does obesity modulate trigeminal nociceptive processing?

Does obesity modulate processing of other sensory modalities?

What are the cellular and molecular mechanisms?
High-Fat Diet Induced Obesity

High Fat Diet (HFD)
45 – 60 %

(Rossi et al, PAIN 2016)
Capsaicin-Induced Trigeminal Sensitization

The effects of Botulinum Toxin type A on capsaicin-evoked pain, flare, and secondary hyperalgesia in an experimental human model of trigeminal sensitization. Gazerani, Parisa; Staahl, Camilla; Drewes, Asbjorn; Arendt-Nielsen, Lars


Subcutaneous Botulinum toxin type A reduces capsaicin-induced trigeminal pain and vasomotor reactions in human skin. Gazerani, Parisa; Pedersen, Natalia; Staahl, Camilla; Drewes, Asbjorn; Arendt-Nielsen, Lars

Capsaicin Induced Trigeminal Sensitization

Intradermal injection
capsaicin

CGRP

V1

V2

V3

Vc

Heather Rossi, PhD
Increased Neuronal Activation in TNC of Obese Mice

Facial injection of capsaicin 0.01%

Fos expression in TNC

Total number of Fos-IR cells in TNC

(Rossi et al, Eur J Pain 2013)
Capsaicin increases ipsilateral facial wipes in a dose dependent manner in obese and lean mice (*$P<0.05$ capsaicin vs vehicle)

(Rossi et al, PAIN 2016)
Affective Pain
Conditioned Place Aversion

Capsaicin 0.01% solution
Topically applied to cornea
Rationale to Stimulate the Cornea

- The cornea is richly innervated by the first branch of the trigeminal nerve
- Same branch that innervates the dura
- Easily accessible without causing injury
Obese Mice are More Sensitive to Capsaicin-induced Pain

Is this outcome relevant to migraine pain?

Trigeminal pain

(Unpublished data)
Light Avoidance Test: Photophobia

Based on a natural conflict paradigm

Innate exploratory behavior

Innate light avoidance (nocturnal animals)

1. Placed light side
2. Moves freely, 20 min.
Obese Mice Are More Photophobic

(Rossi et al. Neuroscience 2016)
Obese Mice Are More Sensitive to Capsaicin-induced Photophobia

(Rossi et al, PAIN 2016)
Photophobia Is Associated with Decreased Locomotor Activity in the Dark Only

(Rossi et al, PAIN 2016)
Is this due to obesity or high-fat diet?
Photophobia Correlates with Weight

Resistant Overweight Obese

RD mean 31 ± 4 g
HFD mean 40 ± 5 g

% Time in Light after Capsaicin

HFD Stratified by Weight

p = 0.0001
Complementary Models of Obesity

HFD-induced obesity

HFD before development of obesity

Genetic obesity without high fat diet

*Rossi et al, PAIN 2016*
HFD without obesity = NO photophobia

Treatment
% Time in Light
BL2 VEH 0.01% Cap 0.1% Cap
one week later
0 20 40 60 80 ob/ob (n=16) CON (n=13)

Obesity without HFD = Photophobia

Treatment
% Time in Light
BL2 VEH 0.01% Cap 0.1% Cap
0 20 40 60 HFD (n=17) R D (n=16)

(Rossi et al, PAIN 2016)
Summary

• Obesity enhances capsaicin-induced activation of TNc neurons

• Trigeminal activation with capsaicin results in clinically-relevant outcomes that can be objectively quantified

• Obesity increases sensitivity to capsaicin-induced photophobia and trigeminal pain (CPA)

• Female mice have a more pronounced phenotype
Concluding Thoughts

• There are multiple animal models of headaches

• Animal models are necessary to explore mechanisms of human disease and develop better therapies

• Clinically-relevant and complementary animal models are needed in basic and translational research

• Sex differences should be systematically assessed in animal models of headache
THANK YOU!!

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