Does my mouse have a headache?

Translational models of migraine

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Outline

• Overview – what is migraine?
• Modeling migraine
  – The attack
  – The aura
• Future directions
  – Integrated models
Features of migraine

Premonitory
- Euphoria/irritability
- Hunger/thirst
- Cognitive

Aura
- Visual
- Somatosensory
  - Language
  - Motor
  - Vestibular/
    Cerebellar?
- Cognitive?
- Arousal?

Attack
- Pain
- Nausea/vomiting
- Conjunctival injection/
  tearing/rhinorrhea
- Flushing/sweating/pallor
- Photophobia
- Phonophobia
- Allodynia

Postdrome
- (and Rebound)
  - Pain
  - Photophobia
  - Phonophobia
  - Allodynia

Interictal
- (Modulation
  Chronification
  Recovery)
- Hormonal
  (Menstruation
  Pregnancy
  Menopause)
- Stress/Affective
  (Anxiety
  Depression)

Comorbidities
- Medication
  overuse
- Trauma
- Infection

Throbbing
unilateral pain

Perspiration
Flushing
Tearing

Phonophobia
Photophobia
Speaks in low voice to avoid aggravating pain
What makes a migraine attack?

**Trigeminovascular Reflex**

**Trigemino-autonomic Reflex**

Pietrobon & Striessnig, *Nat Rev Neurosci* 2003
Pietrobon & Moskowitz, *Annu Rev Neurosci* 2014
Trigeminovascular Physiology, Pharmacology

Sensory stimulation
- mechanical
- thermal
- electrical

Imaging, perfusion measurements
- laser doppler flowmetry
- intravital microscopy
- two photon microscopy

Electrophysiology
- extracellular recordings
- whole cell recordings

*Inflammatory mediators*
- potassium
- bradykinin
- serotonin
- histamine
- ATP
- low pH

Goadsby & Edvinsson Ann Neurol 1993
Strassman et al Nature 1996
Cumberbatch MJ Br J Pharmacol 1999
Oshinsky & Gomonchareonsiri Headache 2007
Noseda Burstein Nat Neurosci 2010
Modeling migraine behavior

Migraine-inducing substances in humans
- nitroglycerin (NTG; NO donor)
- CGRP
- PACAP
-migraine in migraineurs; not in controls
-triptan sensitive

Migraine analog behavior
Acute CGRP ICV reduces time spent in light

Chronic NTG IP reduces mechanical thresholds, topiramate sensitive

Iversen and Olesen Cephalalgia 1996
Olesen and Ashina Trends Pharmacol Sci 2011
Kaiser et al J Neurosci 2012
Pradhan et al Pain 2014
Migraine genetics

Familial migraine
TRESK
Lafraniere et al Nat Med 2010
Casein kinase 1 delta
Brennan et al Sci Transl Med 2013

Susceptibility loci (GWAS)
PRDM16
TRPM8
LRP1
ZNF555
GRM7
MEF2D
ADARB2
ASTN2
TGFBR2
PHACTR1
HTR7
Review:
Schurks J Headache Pain 2012

Familial hemiplegic migraine
DeFusco et al. Nat Genet 2003
Van den Maagdenberg et al. Neuron 2004
Dichgans et al. Lancet 2005
Migraine genetics

**Migraine mouse models**

**Familial migraine**
- TRESK
  - Lafraniere et al. Nat Med 2010
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  - Brennan et al. Sci Transl Med 2013

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- DeFusco et al. Nat Genet 2003
- Van den Maagdenberg et al. Neuron 2004
- Dichgans et al. Lancet 2005
Casein kinase 1 delta (CK1δ) mutations in two families with familial migraine and advanced sleep phase

A. K5231

B. K5579

Alleles not present in >2600 control chromosomes
- thousand genomes database
- CGI 60 whole genomes
- 250 additional controls

Migraine relevant nociception in CK1d mice

Von Frey Hair Threshold

Hargreaves (Radiant Heat) Assay

Increased c-fos immunoreactivity in trigeminal nucleus caudalis

Increased CSD susceptibility and arterial dilation in T44A CK1δ transgenics

Brennan et al, Sci Transl Med 2013
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Throbbing unilateral pain
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Cortical spreading depression and migraine aura

"[scotomata] sketched at brief intervals during an attack suggest that a wave of intense excitation is propagated at a rate of about 3 mm per minute across the visual cortex. This wave is followed by complete inhibition of activity…"

Lashley KS. Arch Neurol Psychiatry 1941


Leao A.A.P., J Neurophysiol 1944

Sugaya E
J Neurophysiol 1975

GCaMP6F, Tx Red Dextran 210x210um, 2.96Hz
How does CSD cause pain?

“Peripheral”

Dura

Surface vessel

Cortex

“Central”

SSN (PPG)

Thalamus

Trigeminal ganglion

Cutaneous Afferents

Trigeminal nucleus caudalis

Zhang et al, *J Neurosci* 2010

Noseda et al, *J Neurosci* 2010
CSD and sensory plasticity

*A network disrupted by spreading depression*

Possible consequences for migraine

**Direct cortical effects**

Phonophobia
Photophobia
Allodynia

**Cortical modulation of lower structures**

Pain
Photophobia
Phonophobia
Allodynia

A mechanism for migraine chronification?

Theriot et al, *J Neurosci* 2012
Effects of CSD at cellular resolution *in vivo*

Two photon microscopy

Whole cell recording

Neuronal calcium and field potential

Astrocyte calcium and field potential

Extracellular glutamate and f.p.

Neuronal membrane potential and Neuronal calcium

Neuronal membrane potential and glutamate
Why is it called cortical spreading depression?  
*What causes the cortical silencing after SD*

Leao A.A.P., *J Neurophysiol* 1944

Punam Sawant
*In vivo* whole-cell recordings (current clamp)
layer 2/3 pyramidal neurons of somatosensory cortex

Suppression of spontaneous synaptic activity after SD
Changes last over an hour

Suppression of synaptic activity after SD
Ratio of excitation/inhibition shifted toward inhibition

Excitatory postsynaptic currents

*Miniature (AP independent)*

Inhibitory postsynaptic currents

*Miniature (AP independent)*

< frequency, > amplitude

Summary

Shift in synaptic balance toward inhibition after SD

An explanation for the depression in spontaneous cortical activity

Leao A.A.P., *J Neurophysiol* 1944

Next: sensory evoked responses
Toward integrated, cellular resolution models
Genetics, physiology, behavior

Awake CSD under two photon

Dynamic head fixed photophobia model
Automated blink detection
Motion through virtual light/dark environment

Behavior: down=quiet, middle=running, grooming, up=motor disruptions
Calcium: GCaMP5G-synapsin

Awake in vivo whole cell, visual stimulation
Conclusions

Does my mouse have a headache?
Trigeminovascular physiology, pharmacology
Migraine relevant stimuli, behavior
Genetic models

Cortical spreading depression
Non-pain measure
Drives pain and other circuit alterations

Toward integrated models
Physiology, behavior, genetics
Cellular resolution
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