CENTRAL MECHANISMS OF MIGRAINE

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MIGRAINE IS PRIMARILY A DISORDER OF THE CENTRAL NERVOUS SYSTEM

• **Clinical symptoms**
  • Premonitory symptoms, aura, and postdrome symptoms are due primarily to changes in the brain

• **Imaging**
  • PET and MRI show changes in activity of cortex, brainstem, hypothalamus before, during, and after migraine headache.

• **Electrophysiology**
  • Various studies showing ictal and interictal changes in cortical excitability in migraine patients
TIMELINE OF A MIGRAINE ATTACK

Onset

PREMONITORY  AURA  HEADACHE  POSTDROME

Neck Pain  Fatigue  Mood change  Light sensitivity  Nausea  Yawning  Polyuria

Vision change  Sensory change  Language change  Cognitive change  Headache  Sound sensitivity  Allodynia

HYPOTHALAMUS  THALAMUS  BRAINSTEM  CORTEX  PERIPHERAL TRIGEMINAL CERVICAL  HYPOTHALAMUS  THALAMUS  BRAINSTEM
HOW CAN HEADACHE BE ASSOCIATED WITH BOTH VASOCONSTRICTION AND VASODILATION?

Vasoconstriction causes release of nociceptive messengers by perivascular nerves (e.g. CGRP, nitric oxide)

Release of nociceptive messengers by perivascular nerves (e.g. CGRP, NO) causes vasodilation

Blood vessel caliber is a marker of the activity of perivascular nociceptive fibers, but not necessarily the cause of pain
“The cerebrovascular trigeminal neuronal system, in which CGRP is the most potent vasoactive constituent, may participate in a reflex or local response to excessive cerebral vasoconstriction that restores normal vascular diameter.”
Migraine pain begins during hypoperfusion phase

Hyperperfusion may outlast pain

Headache is not temporally correlated with either hypo- or hyperperfusion

DILATION OF BLOOD VESSELS IS NEITHER NECESSARY NOR SUFFICIENT FOR CAUSING MIGRAINE PAIN

Cerebral and meningeal blood vessels are *not dilated during* spontaneous migraine or migraine induced by:

- Nitroglycerin
- Sildenafil


Some drugs that induce significant cerebral vasodilation do not cause migraine

- Vasoactive intestinal peptide
Vasoconstriction is not a primary mechanism of acute migraine therapies such as triptans.
DOES EFFICACY OF TRIPTANS AND CGRP ANTAGONISTS FOR MIGRAINE MEAN PERIPHERAL INPUT IS REQUIRED?

NO
Potential Sites of Action of Triptans

**vasculature**

**second order trigeminal neuron**

**periaqueductal gray**

**dural neuropeptide release**

**thalamus**

Adapted from Jones HR. *Netter's Neurology*, St. Louis, MO; Saunders; 2005.
CGRP RECEPTORS ARE PRESENT IN THE CENTRAL NERVOUS SYSTEM

MIGRAINE AND OTHER PRIMARY HEADACHES ARE ASSOCIATED WITH ACTIVATION OF MULTIPLE BRAIN REGIONS

- **Cortex**
  - Waves of change in blood flow and metabolism
  - Increased activation of occipital cortex correlated with photophobia
  - Sustained posterior cortical hypoperfusion

- **Brainstem**
  - Increased blood flow in dorsolateral pons/midbrain

- **Hypothalamus**
  - Increased blood flow before, during, and after headache
  - Increased blood flow in TAC’s

- **Thalamus**
  - Increased activation correlated with somatic allodynia
FLUORESCENCE IMAGING OF INTRACELLULAR Ca$^{2+}$
Cortical Neuronal Culture
CORTICAL "WAVES" IN MIGRAINE WITH AND WITHOUT AURA

Olesen, et al. 1981

Hadjikhani et al., 2001

Cao et al., 1999

Woods et al., 1994
A PET study of photophobia during spontaneous migraine attacks
Denuelle, M; Bouloche, N; Payoux, P; MD, PhD; Fabre, N; Trotter, Y; Geraud, G
CORTICAL MECHANISMS OF MIGRAINE

UNDERLYING PATHOPHYSIOLOGICAL MECHANISMS OF AURA MAY BE CLINICALLY SILENT

ABSENCE OF AURA SYMPTOMS, PARTICULARLY THOSE STRICTLY DEFINED BY ICHD CRITERIA, DOES NOT MEAN THAT CORTICAL PHENOMENA ARE NOT OCCURRING
ACTIVATION OF BRAINSTEM DURING ACUTE MIGRAINE ATTACKS

Weiller et al, Nat Med. 1:658-660; 1995


Can peripheral afferent input modulate migraine?  
YES

Is peripheral afferent input the cause of headache?  
NO
Upper Neck and Head Pain are Referred to the Same Neurons in the Lower Brainstem

Fig. 1. Schematic drawing showing the communicating neural loops between the upper cervical dorsal rami (Cruveilhier plexus). Note the position of the plexus between the overlying semispinalis capitis muscle (cut) and deeper suboccipital triangle muscles (for example, obliquus capitis inferior muscle). Also note the incidence of neural loops, as found in the present study. Printed with the permission of R. S. Tubbs, 2011.
C1 Nerve Root in Migraine?

Patients with migraine have orbital/periorbital pain on C1 Stimulation
Hypothalamic Activation in Migraine

DURING AND AFTER HEADACHE

Activations during migraine attack, before sumatriptan, are shown as statistical parametric maps which show the areas of significant rCBF increases (p<0.001 uncorrected) in colour superimposed on an anatomical reference derived from a T1-weighted MRI. The hypothalamic activation is seen at the point of intersection.

(Denuelle et al., Headache, 2007)

IN PREMONITORY PHASE

Hypothalamic Activation in TACs

May et al., Annals of Neurology 46:791-794; 1999

Thalamic Sensitization in Migraine with Extended Allodynia
Clinical Neurophysiological Studies of Migraine

- Visual, auditory, and somatosensory evoked potential recordings may show reduced habituation between attacks.
- Habituation is normalized immediately preceding and during headache.
- Habituation may be normalized by therapy with migraine preventive medications.

These studies are consistent with alterations in the excitability of cortical, thalamic, and brainstem circuits in migraine.
Somatosensory evoked potential high frequency oscillations are reduced in migraine patients indicating alterations in thalamocortical circuits.
MIGRAINE – A BRAIN “STATE” WITH WIDESPREAD NEUROLOGICAL DYSFUNCTION

AURA

VISUAL SYMPTOMS

SENSORY SYMPTOMS

LANGUAGE SYMPTOMS

COGNITIVE DYSFUNCTION

FATIGUE, MOOD CHANGE

NAUSEA, VOMITING

Light, sound smell sensitivity

HEADACHE

MOTOR DYSFUNCTION

YAWNING, POLYURIA

DIZZINESS, VERTIGO

Cutaneous Allodynia
SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX

ARISTIDES A. P. LEÃO

Department of Physiology, Harvard Medical School, Boston, Massachusetts

(Received for publication August 14, 1944)
CORTICAL SPREADING DEPRESSION (CSD) – WHAT IS IT?

- Wave of activation followed by suppression of activity that spreads across the brain surface

- Includes
  - Massive depolarization of neurons and glial cells, followed by suppression of spontaneous activity
  - Marked neurochemical and ionic changes. Glutamate and K+ play key roles
  - Dramatic changes in vascular function and brain perfusion.
In Vivo Optical Intrinsic Signal Imaging in Mouse
CSD evoked by KCl pulse --- mouse cortex. 5 minute recording

OPTICAL IMAGING OF CORTICAL SPREADING DEPRESSION
EXPERIMENTAL TRIGGERS
- Electrical stimulation, KCl
- Glutamate, Ouabain
- Emboli, Endothelin
- Astrocyte Activation

HUMAN TRIGGERS
- SAH
- Stroke
- Brain Injury

MODULATORS
- FHM mutations
- Migraine mutations
- Sex, Hormones

↑ K+, Glutamate

CORTICAL SPREADING DEPRESSION

EXTRACELLULAR SPACE
- Cellular volume changes
- ↑ extracellular K+, glutamate, ATP, nitric oxide
- ↓ Na+

ASTROCYTE RESPONSE
- Depolarization
- Calcium waves
- K+ Influx/Efflux
- Release of ATP, eicosanoids

NEURONAL RESPONSE
- Depolarization
- Cellular Swelling
- Ion fluxes

VASULAR RESPONSE
- Dilation
- Constriction
- Vascular/metabolic uncoupling

EXTENSION OF ISCHEMIC INJURY

MIGRAINE AURA

ACTIVATION OF TRIGEMINAL AFFERENTS

THALAMIC/BRAINSTEM ACTIVATION

HEADACHE
EVIDENCE THAT CSD IN RODENT MODELS IS A VALID MODEL FOR MIGRAINE

• Genetic alterations associated with familial hemiplegic migraine, and migraine with and without aura, alter CSD

• CSD is altered by sex and ovarian hormones

• Multiple migraine preventive medications inhibit CSD
BRAIN CELL TYPES

NEURONS

VASCULAR CELLS
- Endothelial cells
- Smooth muscle
- Pericytes

EPENDYMAL CELLS

MENINGEAL CELLS

GLIAL CELLS
CENTRAL NERVOUS SYSTEM CELLS
GLIAL CELL TYPES

CENTRAL NERVOUS SYSTEM
- ASTROCYTES
- OLIGODENDROCYTES
- MICROGLIA

PERIPHERAL NERVOUS SYSTEM
- SCHWANN CELLS
- SATELLITE CELLS
Selective stimulation of astrocytes can trigger CSD
VASCULAR CELLS RELEASE DIFFUSIBLE MESSENGERS THAT MAY INFLUENCE ACTIVITY OF NEIGHBORING NEURONS AND GLIAL CELLS
SUSTAINED NEUROVASCULAR UNCOUPLING WITH CORTICAL SPREADING DEPRESSION

Chang et al., Brain 2010
VASCULAR RESPONSE TO SPREADING DEPRESSION IN HUMANS WITH BRAIN INJURY IS VARIABLE

COULD VARIABILITY IN VASCULAR RESPONSE TO SPREADING DEPRESSION GENERATE VARIABILITY IN SYMPTOMS?

Dreier et al, Brain 2009.
Activation of Meningeal Nociceptors by Cortical Spreading Depression: Implications for Migraine with Aura

XiChun Zhang,1 Dan Levy,1 Rodrigo Nosed,1 Vanessa Kainz,1 Moshe Jakubowski,1 and Rami Burstein1,2
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The Journal of Neuroscience, June 30, 2010 • 30(26):8837–8847 • 8887
SUSTAINED NEUROVASCULAR UNCOUPLING IN MIGRAINE?

Denuelle et al.,
Cephalalgia 2008
PROLONGED AURA IN HEMIPLEGIC MIGRAINE CAN BE ASSOCIATED WITH HYPO and HYPER PERFUSION OF THE HEMISPHERE CORRELATED WITH WEAKNESS, AND HYPER PERFUSION OF THE CONTRALATERAL HEMISPHERE

Iizuka T et al. J Neurol Neurosurg Psychiatry 2012;83:205-212
Headache is associated with chronic changes in brain structure and function.
Areas of Reduced Brain Volume in Patients with Migraine

Migraine patients have decreased gray matter density or volume in structures in the “pain matrix” involved in descending pain modulation.

- Cingulate cortex
- Insula
- Prefrontal cortex
- Amygdala
- Parietal cortex
- Superior temporal gyrus and temporal pole


Migraine Patient May Show Increased Brain Volume In Other Brain Regions

Migraine vs. control

Migraine with Aura vs. Without Aura


Increased volume in dorsolateral pons/midbrain in migraine patients with white matter lesions
Functional and structural changes – are any specific to headache?
Similar Changes in the “Pain Matrix” have been observed in:

- Tension type headache
- Fibromyalgia
- Osteoarthritis
- Chronic neuropathic pain
- Chronic gastrointestinal pain
- Phantom pain
CHANGES IN BRAIN VOLUME ARE **REVERSIBLE**

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**Brain Gray Matter Decrease in Chronic Pain Is the Consequence and Not the Cause of Pain**

Res Rodriguez-Raecke, Andreas Niemeyer, Kristin Ible, Wolfgang Ruether, and Arne May

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13746 - The Journal of Neuroscience, November 4, 2009 - 29(44):13746 - 13750
MODULATING FACTORS
- Genes
- Gender/Hormones
- Ionic/Metabolic
- Drugs
- Environment

CORTICAL WAVES
- CSD
- Astrocyte waves
- Vascular waves

↑ BBB Permeability

DYSREGULATION OF CORTICAL, BRAINSTEM, HYPOTHALAMIC, THALAMIC EXCITABILITY

NOCICEPTIVE ACTIVATION
- Vasoconstriction
- Vascular/metabolic uncoupling
- Release of CGRP, PACAP, NO, ATP
- Vasodilation

HEADACHE
- SENSORY SENSITIVITY
  - Photo/phonophobia
  - Cutaneous allodynia
  - Nausea
  - Vertigo
  - Fatigue
  - Mood change

PRODROMAL SYMPTOMS
- Yawning
- Polyuria
- Neck pain

BRAINSTEM/HYPOTHALAMIC/THALAMIC ACTIVATION AND SENSITIZATION
- Trigeminal nucleus caudalis
- Periaqueductal gray
- Other brainstem nuclei

AURA
- Visual
- Sensory
- Cognitive
MIGRAINE

Reduced Brain Volume in Areas Involved in Descending Pain Modulation

Alteration in Brain Volume in Areas Involved in Vision Processing

Increases in Brain Iron in Red Nucleus, Basal Ganglia

Posterior Circulation Strokes

White Matter Lesions

MEDICATION OVERUSE

Hypo/hypermetabolism In multiple brain regions

Altered functional responses in pain processing regions

CHRONIC BRAIN CHANGES IN MIGRAINE
HEADACHE THERAPEUTIC TARGETS

Central Pain Matrix

Central and Peripheral Stimulation

Brainstem
- Glutamate receptors
- 5HT receptors
- CGRP
- NO
- PACAP
- Opioid receptors

Cortical Excitability
- Glutamate receptors
- Na+/K+ ATPase
- Ion Channels
- Adenosine receptors

Distinct Neuronal, Glial and Vascular Components

Peripheral Nociception
- Peptide receptors
- Purinergic receptors
- Ion Channels

Adapted from Jones HR. Netter's Neurology, St. Louis, MO; Saunders; 2005.