Migraine; An Anatomic and Physiological Basis

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MIGRAINE PATHOPHYSIOLOGY

- Genetic basis
- The sensitive brain
- Triggering migraine
- The migraine aura
- Migraine pain and the features of the acute attack

THE P/Q GENE PRODUCT

THE GENETIC BASIS

FHM1
P/Q channel
Presynaptic Voltage gated Occipital Cortex Trigeminal nucleus Caudalis

FHM2
Linkage to Chromosome 1 Na-K ATP

FHM3
Na Channel

Genetic Predisposition: Familial Hemiplegic Migraine

- FHM: a rare inherited form of migraine
- Genetically heterogeneous autosomal dominant!

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHM-1</td>
<td>CACNA1A</td>
<td>P/Q Ca²⁺ channels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ presynaptic Ca²⁺</td>
</tr>
<tr>
<td>FHM-2</td>
<td>ATP1A2</td>
<td>Na⁺K⁺-ATPase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ K⁺ and glutamate clearance</td>
</tr>
<tr>
<td>FHM-3</td>
<td>SCN1A</td>
<td>Na⁺ channel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent Na⁺ influx</td>
</tr>
</tbody>
</table>

FHM = familial hemiplegic migraine.
**Interictal**

- Channelopathy/ Genetics
- Brain/occipital cortex hyperexcitability
- Mitochondrial defect
- Magnesium deficiency

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**PWI: Persistent Visual Aura**

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fMRI During Spontaneous MwA


Initiating Mechanisms of Headache Pain: Cortical Spreading Depression

- Wave of intense cortical neuron activity
  - 1/CBF
  - Followed by neuronal suppression
    - ↓ CBF
    - Often coincides with headache onset
- Velocity: 2–3 mm/min
- Underlies visual aura
- Occurs in clinically silent areas of the cortex?
- Migraine without aura

THE NEUROVASCULAR THEORY

Migraine is a neurovascular pain syndrome

- Referred pain from dura mater and blood vessels
- Peripheral neural processing
  - Neurogenic plasma protein extravasation (PPE)
  - Neuropeptides
- Central neural processing

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Brain Stem Involvement in Migraine

- Brain stem aminergic nuclei can modify trigeminal pain processing
- PET demonstrates brain stem activation in spontaneous migraine attacks
- Brain stem activation persists after successful headache treatment
- Brain stem: generator or modulator?

PET=positron emission tomography.

Which Structure is Involved?

PAG

Chronic Daily Headache; Denovo

Automated Segmentation of Brain Tissue

Correlation of Iron in PAG with Longevity of Migraine

Bolay et al. Nat Med 2002

Laser Speckle contrast image
Trigeminovascular Migraine Pain Activation


CSD produces Pain

Activation of the Trigeminovascular System: Physiologic Impact
The Trigeminovascular System

5-HT1 & migraine

- 5-HT1B \(\rightarrow\) constriction
- 5-HT1D \(\rightarrow\) PPE inhibition; TNC inhibition
- 5-HT1F \(\rightarrow\) PPE inhibition; TNC inhibition

iNos in Migraine

- Nitric Oxide (NO) = key physiological mediator in the body (neurotransmission & vasodilatation)
- L-arginine nitric oxide synthases (NOS) Nitric oxide (NO)
- Three NOS isoforms:
  - eNOS (endothelial NOS) - CV system
  - nNOS (neuronal NOS) - neurotransmission
  - iNOS (inducible or inflammatory NOS) - promotes tissue pathology

* Readily induced upon inflammation or tissue injury
* Triggers pathological vasodilatation and edema
* Sensitizes nerve terminals and causes hyperalgesia
* Promotes cytokine production and induces COX1 & 2

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Peripheral sensitization in Migraine

- Activated TGVS nociceptors release CGRP and substance P
- NO also released
- Leads to
  - Vasodilation
  - CGRP, NO, substance P
- Mast cell degranulation
  - CGRP, substance P
- Plasma extravasation
  - substance P

Meningeal blood vessel

Cutaneous allodynia

Throbbing pain

Pain perception

Central Sensitization in Migraine

- Sensitized Central neuron
- Sensitized Peripheral neuron
- Sensitized Central neuron

Meningeal blood vessel

Sensitized Central neuron (thalamus)

Meningeal blood vessel

Sensitized Central neuron (spinal cord)

Sensitized Peripheral neuron (trigeminal ganglion)
Pain modulation

Neurotransmitters that modulate nociceptive processing

- Ach
- Norepinephrine
- Serotonin
- Dopamine
- Glutamate
- Anandamide/CB₁
- CCK
- GABA
- Adenosine
- Glycine
- Endogenous opioids

Glutamate (Glu)
**Glutamate in Migraine**  
**Supporting observations**

- Localization experiments
- Support from functional studies
  - activation of TNC cells by L-Glu
  - Glu release following TNC stimulation
  - activation/propagation of CSD by Glu
  - Increase nNOS activity by GluR activation
  - Release of SP following NMDA activation

*Ramadan, 2003*