One Hundred Years of Migraine Research
Major Clinical and Scientific Observations
From 1910 to 2010

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New era of migraine (1980-1990)

All images have been obtained from freely available internet sites

• A new headache classification
  Classification Committee of the IHS, 1988

• A new drug for migraine - the discovery of Sumatriptan
  Humphrey et al, 1988

• Migraine and calcitonin gene-related peptide
  Goadsby and Edvinsson, 1990
Development of ICHD

1962  Ad Hoc Committee on Classification of Headache.
1978  Olesen proposed a diagnostic classification of headache disorder.
1988  The ICHD was published.
       ♦ Operational diagnostic criteria.
1992  The ICHD was adopted by WHO into ICD-10.
2004  The ICHD-II was published.
       ♦ Typical aura could be followed by either migraine headache or just headache.
       ♦ Sporadic hemiplegic migraine as a new subtype of migraine with aura.
       ♦ Chronic migraine as a complication of migraine.
2006  The criteria for chronic migraine revised.
<table>
<thead>
<tr>
<th>1.1 Migraine without aura</th>
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<td>1.2 Migraine with aura</td>
<td>1.2 Migraine with aura</td>
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<td>1.2.1 Migraine with typical aura</td>
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<td>1.2.4 Familial hemiplegic migraine</td>
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<td>1.5.1 Benign paroxysmal vertigo of childhood</td>
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<td>1.3.3 Benign paroxysmal vertigo of childhood</td>
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<td>1.4 Retinal migraine</td>
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<td>1.6.1 Status migranosus</td>
<td>1.5.1 Chronic migraine</td>
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<td>1.6.2 Migrainous infarction</td>
<td>1.5.2 Status migranosus</td>
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<tr>
<td>1.7 Migrainous disorder not fulfilling above criteria</td>
<td>1.5.3 Persistent aura without infarction</td>
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<td>1.3 Ophthalmoplegic migraine</td>
<td>1.5.4 Migrainous infarction</td>
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<td>1.6 Probable migraine</td>
<td>1.5.5 Migraine triggered seizures</td>
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<tr>
<td>1.6.1 Probable migraine without aura</td>
<td>1.6.2 Probable migraine with aura</td>
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<td>It was excluded.</td>
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Table 8
Headaches that were included in the new classifications

IHS classifications – 1988

- Cyclical vomiting
- Chronic migraine
- Chronic paroxysmal hemicrania
- Hypnic headache
- Hemicrania continua

→

Typical aura with non-migraine headache
- Abdominal migraine
- Migraine triggered seizures
- SUNCT syndrome
- Primary thunderclap headache
- New daily persistent headache

IHS classifications – 2003
A New Drug for Migraine
The Discovery of Sumatriptan
1960 Intravenous serotonin (5-HT) was effective in the treatment of migraine, but many adverse events.

1967 Serotonin depletion from blood platelets during migraine attacks.

1980+ Identification of an unknown serotonin receptor type (now called 5-HT1B) that is largely located in cranial rather than peripheral blood vessels.

1984 Development of the first 5-HT1B agonists—sumatriptan.
The Discovery and Development of the Triptans, a Major Therapeutic Breakthrough

Patrick P.A. Humphrey, PhD, DSc, OBE

The drug discovery programs that led to the development of the triptans were determined by the membership of the American Headache Society to be the most important breakthrough in headache medicine in the last 50 years. Dr. Humphrey, who spearheaded the drug discovery, recounts the pioneering work that took place and examines its therapeutic impact.

Headache; 48:685-687

Dr. Humphrey was until recently the Executive Vice President of Research at Theravance Inc., South San Francisco, California. Dr. Humphrey’s pioneering drug discovery work led to the development of sumatriptan.

The triptans are a class of drug specifically designed and developed for the acute treatment of migraine. All aggressively continue with their endeavors, without the previously inevitable day-off sick. Sumatriptan also proved to be
Role of serotonin

- serotonin (released from brainstem serotonergic nuclei) plays a role in the pathogenesis of migraine,
  - perhaps mediated by its direct action upon the cranial vasculature,
  - by its role in central pain control pathways,
  - or by cerebral cortical projections of brainstem serotonergic nuclei.
- tricyclic antidepressants, which block serotonin reuptake, are effective antimigraine prophylactic agents.
- more SSRIs are not very effective in migraine prevention.
- low serotonin state may result in a deficit in the serotonin descending pain inhibitory system, facilitating activation of the trigeminovascular nociceptive pathways in conjunction with cortical spreading depression.
Serotonin, methyergide and triptan

- Serotonin- vasoconstrictor for all vessels.
- Methyergide- selectively constrictor effect in the dog carotid bed and femoral vein. The “atypical” 5-HT receptor (5-HT1B) was suggested.
- Ketanserin (5-HT2 antagonist) did not antagonize the effect of 5-CONH$_2$T (5-hydroxaminotryptamine, a potent selective 5-HT agonist) in dog saphenous vein.
- 5-CONH$_2$T has only a weak effect on rabbit isolated aorta, but was a potent agonist in dog saphenous vein.
- The triptans are relatively cranioselective when compared the effect on coronary arteries.
The process of migraine pain

When the trigeminal system is activated (1), peptides are released (2) prompting an inflammatory reaction. This increases flow of sensory traffic through the brain stem (3), the thalamus and ultimately the cortex (4).
"specific" therapies for acute migraine

- Triptans inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem
- Triptans inhibit transmission in the trigeminal nucleus caudalis (TNC), thereby blocking afferent input to second order neurons; this effect is probably mediated by reducing the levels of calcitonin gene related peptide (CGRP).
- Triptans may also activate serotonin receptors in descending brainstem pain modulating pathways and thereby inhibit dural nociception.
Figure 2. Possible Sites of Action of Triptans in the Trigeminovascular System.

Goadsby PJ, Lipton RB and Ferrari MD, NEJM 2002;346:257-270
## Ergots vs. Triptans

<table>
<thead>
<tr>
<th>5-HT</th>
<th>Ergots</th>
<th>Triptans</th>
<th>Dysphoria</th>
<th>Nausea / Emesis</th>
<th>Anti-migraine</th>
<th>Peripheral Vascular Effects</th>
<th>Asthenia</th>
<th>Dizziness</th>
<th>GI / Nausea / Emesis</th>
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Triptan/Ergot
Contraindication and Adverse Events

- Contraindication
  - ischemic heart disease
  - uncontrolled HTN
  - basilar or hemiplegic migraine
  - pregnancy
  - MAO-I use

- Adverse Events
  - paresthesia, tingling
  - flushing, burning, or warm/hot sensation
  - dizzy, somnolence, fatigue, heaviness
Cardiovascular Safety of Triptans

- Incidence of serious cardiovascular events is extremely low.
- Risk-benefit profile favors use in the absence of vascular risk factors.
  - Triptan cardiovascular safety expert panel of the American Headache society – consensus statement
    Headache 44(5):414, 2004
Migraine and Calcitonin Gene-Related Peptide (CGRP)
calcitonin gene-related peptide (CGRP)

- Widely expression in
  - Heart
  - Blood vessels
  - Pituitary
  - Thyroid
  - Lung
  - GI tract

- Biological effect
  - Neuromodulation
  - Vasodilatation
  - Cardiac contractility
  - Bone growth
  - Mammalian development

- Released from motor neurons at the neuromuscular junction and sensory neurons of spinal cord.
- 2 isoforms:
  - $\alpha$ CGRP is present in the sensory neurons
  - $\beta$ CGRP is mainly present in the enteric nervous system.
CGRP- A neuropeptide, present in perivascular nerves of cerebral arteries and trigeminal ganglia nerves, is a potent vasodilator of cerebral and dural vessels.

Stimulation of the trigeminal ganglion induces the release of CGRP, substance P & VIP and CGRP infusion can trigger a migraine attack in migraineurs.

CGRP may mediate trigeminovascular pain transmission from intracranial vessels to the central nervous system, as well as the vasodilatory component of neurogenic inflammation. However, the evidence is conflicting.

Although one study found elevation of CGRP levels in EJV during migraine attack, this result was not reproduced in a subsequent study. In addition, CGRP did not activate or sensitize meningeal nociceptors in an animal model.

Elevated CGRP levels are normalized in patients with migraine following administration of the sumatriptan, suggesting that triptans may control migraine at least in part by blocking the release of CGRP.

VIP: vasoactive intestinal peptide;  EJV: external jugular vein.
CGRP: Central role in migraine

- Highly expressed in both the peripheral and central nervous systems
- Contained in nerve fibers innervating all organs and tissues, including vasculature, skin, muscles
  - Olfaction, audition, learning, feeding, autonomic functions, motor activity, nociception, and vasodilation
- Originally thought to contribute to migraine strictly through its vasodilatory actions
  - Early theories viewed migraine as a vascular disorder
- Then speculated to be involved in peripheral inflammation
  - The neurogenic inflammation theory of migraine
- Currently considered to be a neuropeptide involved in the transmission of migraine pain and induction of the pronociceptive stage
  - The neuronal origin of migraine.
CGRP First Identified as a Potential Mediator of Trigeminal Inflammation

- CGRP, a 37-amino-acid peptide, was first discovered as a potent vasodilator.
- Initially considered important in migraine because of its potential peripheral actions:
  - Vasodilation
  - Neuroinflammation

Pain Signaling to CNS

CGRP: Central Role in Migraine

- CGRP involved in many steps of migraine pathophysiology

1. Pain transmission and induction of the pronociceptive state
   - At the ganglion
   - At the caudalis

2. Potential actions at many other sites of the brain

3. Peripherally: inflammation and vasodilation

Trigeminovascular Migraine Pain Pathway

Preventive medication target

Central Sensitization

Neuropeptide Release

5-HT_{1D} Receptors
Vasoconstriction

5-HT_{1D} Receptors
Trigeminal Inhibition

Vasodilatation

Acute medication target

Proposed Mechanisms of Migraine

Abnormal cortical Activity:
Hyperexcitable brain
(5HT↓, Ca↑, Glu↑, Mg↓)

Cortical Spreading Depression

Activation/Sensitization of TGVS

Vasodilation
Neurogenic Inflammation
peripheral sensitization

Abnormal brainstem Function:
Excitation of brainstem, PAG, etc

Central Sensitization

Headache Pain

TGVS=trigeminal vascular system.
- Development of migraine headache depends on the activation of these afferents.
- Activation of the meningeal trigeminovascular afferents leads to activation of second-order dorsal horn neurons in the trigeminal nucleus pars caudalis (TNC).
- Impulses are then carried rostrally to brain structures that are involved in the perception of pain, including several thalamic nuclei and the ventrolateral area of the caudal periaqueductal grey region (PAG).
New drugs for acute migraine

Table 1. Emerging therapies for acute migraine

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Treatment class</th>
<th>Clinical phase</th>
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<tbody>
<tr>
<td>COL-144</td>
<td>5-HT_{1F} receptor agonist</td>
<td>Phase II–complete</td>
</tr>
<tr>
<td>Telcagepant (MK-0974)</td>
<td>CGRP receptor antagonist</td>
<td>Phase III–complete</td>
</tr>
<tr>
<td>BI 44370</td>
<td>CGRP receptor antagonist</td>
<td>Phase II–complete</td>
</tr>
<tr>
<td>BGG492</td>
<td>AMPA receptor antagonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>Tezampanel (LY-293558)</td>
<td>AMPA and kainate receptor antagonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>LY466195&lt;sup&gt;a&lt;/sup&gt;</td>
<td>GLUK5 kainate receptor antagonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>SB-705498</td>
<td>TRPV1 receptor antagonist</td>
<td>Phase II–complete</td>
</tr>
<tr>
<td>NXN-188</td>
<td>Neuronal nitric oxide synthase (nNOS) inhibition &amp; 5-HT_{1B/D} agonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>GW274150</td>
<td>Inducible nitric oxide synthase inhibition</td>
<td>Phase II–complete</td>
</tr>
<tr>
<td>BGC20-1531</td>
<td>Prostanoid EP4 receptor antagonist</td>
<td>Phase II, phase I</td>
</tr>
</tbody>
</table>

<sup>a</sup>Not yet listed on the ClinicalTrials.gov website

*AMPA* α-amino-3-hydroxy-5-methyl-4-isozolepropionic acid, *CGRP* calcitonin gene-related peptide, *TRPV1* transient receptor potential vanilloid subfamily member 1
Thank you

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