

# **Pathophysiology of Migraine**

# MIGRAINE PATHOPHYSIOLOGY: *A NEUROVASCULAR HEADACHE*

## Objectives

- Review the neurobiology of migraine
  - Features of acute attack
  - neuroanatomical substrates
- Discuss the current understanding of migraine, vulnerability, initiation and activation of the trigeminocervical pain system
- Describe the modulation of head pain in the CNS



## WHAT IS MIGRAINE?

- Neurobiologically based, common clinical syndrome characterized by recurrent episodic attacks of head pain which serve no protective purpose
- The headache is accompanied by associated symptoms such as nausea, sensitivity to light, sound, or head movement
- The vulnerability to migraine is for many, an inherited tendency

Migraine is a complex neurobiological disorder that has been recognized since antiquity. Many current books cover the subject in great detail.

The core features of migraine are headache, which is usually throbbing and often unilateral, and associated features of nausea, sensitivity to light, sound, and exacerbation with head movement. Migraine has long been regarded as a *vascular* disorder because of the throbbing nature of the pain. However, as we shall explore here, vascular changes do not provide sufficient explanation of the pathophysiology of migraine. Up to one-third of patients do not have throbbing pain. Modern imaging has demonstrated that vascular changes are not linked to pain and diameter changes are not linked with treatment.

This presentation aims to demonstrate that:

- Migraine should be regarded as *neurovascular* headache.
- Understanding the anatomy and physiology of migraine can enrich clinical practice.

Lance JW, Goadsby PJ. *Mechanism and Management of Headache*. London, England: Butterworth-Heinemann; 1998.

Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. 2nd ed. London, England: Martin Dunitz; 2002.

Olesen J, Tfelt-Hansen P, Welch KMA. *The Headaches*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

# MIGRAINE PATHOPHYSIOLOGY

## ■ *Neuroanatomical correlates of the migraine attack*

■ Vulnerability to migraine

■ Triggering migraine

■ Migraine aura

■ Migraine pain



The frequency with which migraine attacks occur may vary from once in a lifetime to almost daily, an indication that the degree of migraine predisposition varies individually. Our current concept is of a threshold of susceptibility.

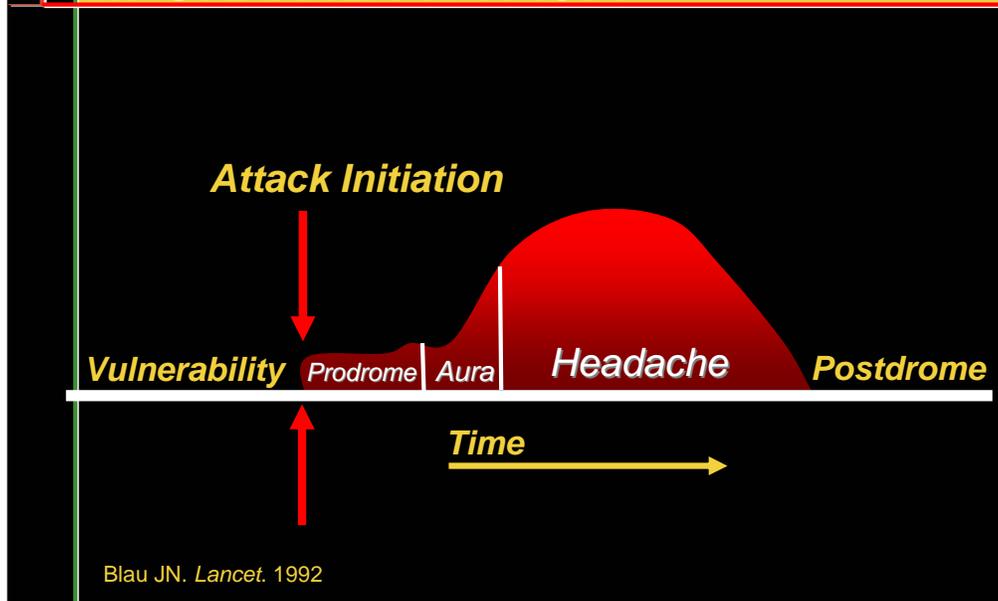
To understand migraine, we need to consider both the factors that influence the threshold of a person's susceptibility to a migraine attack and also the mechanisms that trigger the attack and the associated symptoms. Theories about pathophysiology must be based on the anatomy and physiology of the pain-producing structures within the cranium.

First we will consider the neuroanatomical structure underlying the migraine syndrome. Next we will discuss the genetic basis of vulnerability to migraine and the functional consequences of inheriting migrainous genes, which might be called a "sensitive brain."

We will also talk about the triggers for migraine, how these explain aspects of the disorder, and how this knowledge translates into practical, rational, lifestyle advice when planning treatment.

We shall consider our current understanding of the migraine aura, migraine pain and features of the acute attack.

## CLINICAL PHASES OF A MIGRAINE ATTACK



Acute migraine attacks occur in the context of an individual's inherent level of vulnerability. The greater the vulnerability or lower the threshold, the more frequent attacks occur. Attacks are initiated when internal or environmental triggers are of sufficient intensity to activate a series of events which culminate in the generation of a migraine headache. We are all too familiar with the clinical phases of a migraine attack. Many migraineurs experience vague vegetative or affective symptoms as much as 24 hours prior to the onset of a migraine attack. This phase is called the **prodrome** and should not be confused with the aura phase.

The **aura** phase consists of focal neurological symptoms that persist up to one hour. Symptoms may include visual, sensory, or language disturbance as well as symptoms localizing to the brainstem.

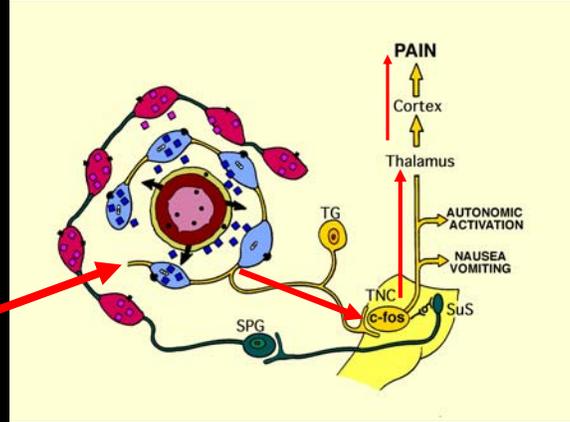
Within an hour of resolution of the aura symptoms, the typical migraine **headache** usually appears with its unilateral throbbing pain and associated nausea, vomiting, photophobia, or phonophobia. Without treatment, the headache may persist for up to 72 hours before ending in a **resolution phase** often characterized by deep sleep.

For up to twenty-four hours after the spontaneous throbbing has resolved, many patients may experience malaise, fatigue, and transient return of the head pain in a similar location for a few seconds or minutes following coughing, sudden head movement, or valsalva movements. This phase is sometimes called the migraine **hangover**.

Blau JN. Migraine: theories of pathogenesis. *Lancet*. 1992;339:1202-1207.

## ACTIVATION OF TRIGEMINAL/ CERVICAL AFFERENT NEURONS

Vulnerability  
↓  
Attack Initiation  
(Prodrome/Aura)  
↓  
**PAIN**



Somatosensory input to the head involves pseudounipolar trigeminal and upper cervical branches

Investigations in migraine fall into three categories:

1. Those focused on the vulnerability for an attack and the generation of the acute attack
2. Those focused on activation of the trigeminal/cervical pain system, and
3. Those examining the modulation of the painful activation within the CNS.

This diagram summarizes the flow of nociceptive information into the CNS when activation occurs within primary afferent neurons.

# MIGRAINE PATHOPHYSIOLOGY

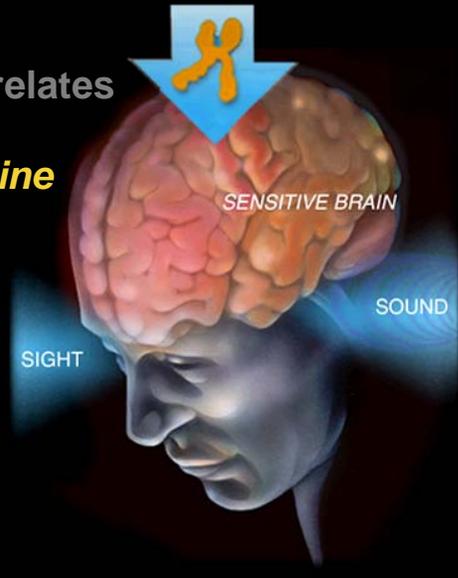
- Neuroanatomical correlates

- ***Vulnerability to migraine***

- Triggering migraine

- Migraine aura

- Migraine pain



It is becoming increasingly clear that much of the vulnerability to migraine is inherited.

## VULNERABILITY: GENETIC BASIS

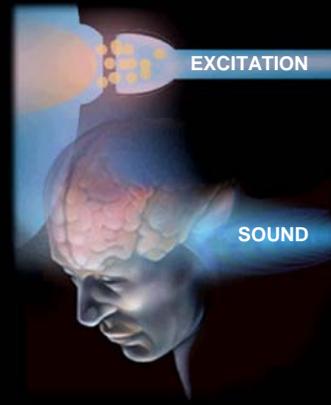
Twin studies: MZ > DZ

Ion channelopathy –

### Familial hemiplegic migraine

- $\alpha_{1A}$  subunit of the P/Q voltage-gated  $Ca^{2+}$  channel on chromosome 19 (~50% of cases)
- Mutation in gene *ATP1A2* (encodes alpha2 subunit of  $Na^+/K^+$  pump) results in loss of function of single *ATP1A2* allele (chromosome 1)
- Linked to regular migraine

Genetically heterogeneous



A strong familial influence in migraine has long been apparent and this has been demonstrated in twin studies. The concordance for migraine in monozygotic twins is greater than that for dizygotic twins (1). However, it is also clear that the genetic background is complex.

The molecular genetic era for migraine was heralded by the identification of four different missense mutations in the  $\alpha_{1A}$  subunit of the P/Q-type, voltage-gated calcium channel on chromosome 19 that is responsible for familial hemiplegic migraine (FHM) in some families (2). FHM is a rare subtype of migraine with aura that has a clear autosomal dominance inheritance pattern. A linkage to chromosome 19 also appears to occur in some families with more usual migraine (3,4).

De Fusco and colleagues (5) show that the gene *ATP1A2*, which encodes the alpha2 subunit of the  $Na^+/K^+$  pump, is associated with familial hemiplegic migraine type 2 (FHM2) and is linked to chromosome 1q23. This mutation results in a loss of function of a single allele of *ATP1A2*. This is the first report that associates a mutation in the  $Na^+/K^+$  pump to the genetics involved in migraine.

Additionally, research suggests that variations within the dopamine D2 receptor gene also may have some affect on susceptibility to migraine (6). Thus, genetic studies are providing important information about the molecular basis of migraine.

1. Honkasalo ML, Kaprio J, Winter T, et al. Migraine and concomitant symptoms among 8167 adult twin pairs. *Headache*. 1995;35:70-78.

2. Ophoff RA, Terwindt GM, Vergouwe GM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the  $Ca^{2+}$  channel gene *CACNL1A4*. *Cell*. 1996;87:543-552.

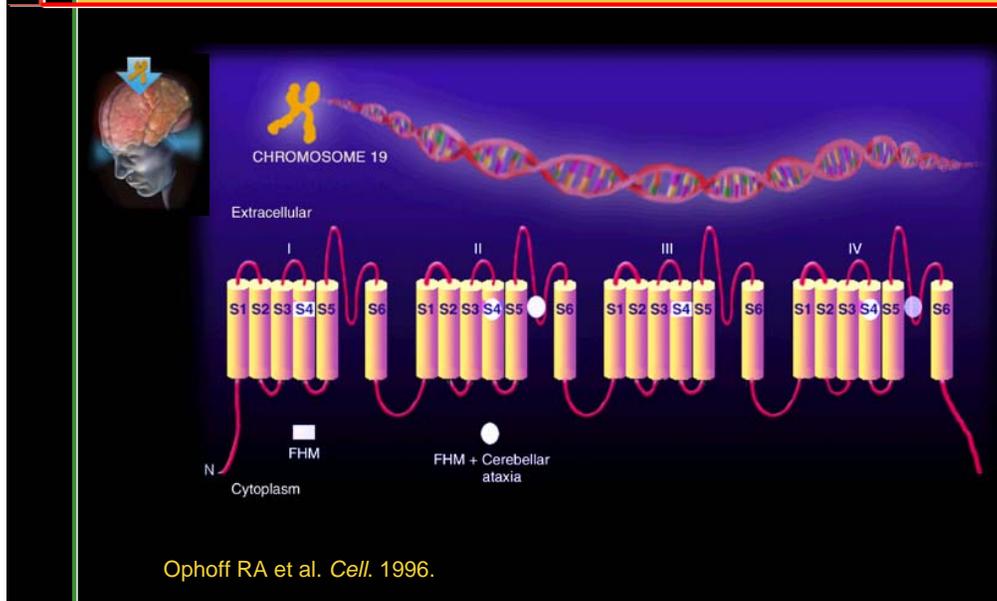
3. May A, Ophoff, RA, Terwindt GM, et al. Familial hemiplegic migraine locus on chromosome 19p13 is involved in common forms of migraine with and without aura. *Hum Genet*. 1995;96(5):604-608.

4. Nyholt DR, Lea RA, Goadsby PJ, et al. Familial typical migraine: linkage to chromosome 19p13 and evidence for genetic heterogeneity. *Neurology*. 1998;50:1428-1432.

5. De Fusco M, Marconi R, Silvestri L, et al. Haploinsufficiency of *ATP1A2* encoding the  $Na^+/K^+$  pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet*. 2003;33(2):192-196.

6. Peroutka SJ, Wilhoit T, Jones K. Clinical susceptibility to migraine with aura is modified by dopamine D2 receptor (*DRD2*) *NcoI* alleles. *Neurology*. 1997;49:201-206.

# THE P/Q GENE PRODUCT



This diagram illustrates the four missense mutations in the  $\alpha_1$  subunit of the P/Q-type, voltage-gated calcium channel on chromosome 19 causing FHM in some families, as well as mutations responsible for episodic ataxia type 2 (1). This discovery has important implications for the pathophysiology of migraine. Neuronal calcium channels mediate serotonin (5-HT) release within the midbrain (2).

Therefore, dysfunction of these channels might impair serotonin release and predispose patients to migraine or impair their self-aborting mechanism. The interactions of magnesium with calcium channels are also interesting in light of magnesium deficiency in the cortex of migraine patients and the role of calcium channels in spreading depression, which may initiate migraine aura (3).

1. Ophoff RA, Terwindt GM, Vergouwe GM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca<sup>2+</sup> channel gene CACNL1A4. *Cell*. 1996;87(3):543-552.
2. Yakhnitsa VA, Pilyavskii AI, Limansky YP, Bulgakova NV. Modulation of the activity of midbrain central gray substance neurons by calcium channel agonists and antagonists in vitro. *Neuroscience*. 1996;70(1):159-167.
3. Ramadan NM, Halvorson H, Vande-Linde A, et al. Low brain magnesium in migraine. *Headache*. 1989;29(9):590-593.

# MIGRAINE PATHOPHYSIOLOGY

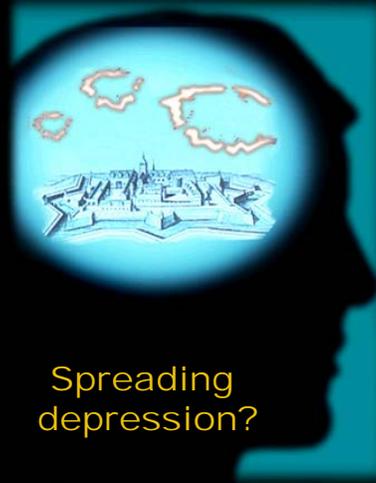
- Neuroanatomical correlates

- Vulnerability to migraine

- **Triggering migraine**

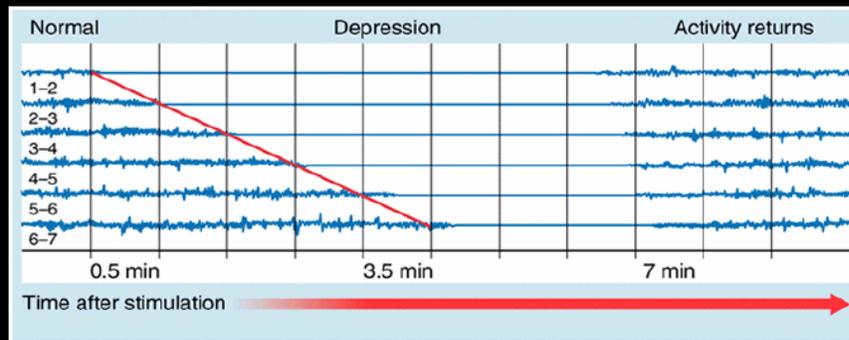
- Migraine aura

- Migraine pain



Given the genetic tendency to headache that results in a heightened sensitivity to stimuli of many types in people with migraine, how can we turn this into practical information about avoiding headache triggers ?

## SPREADING DEPRESSION OF LEAO



Silberstein SD et al. *Headache in Clinical Practice*. 2002; Leao AAP. *J Neurophysiol*. 1994.

This EEG illustrates spreading depression moving across the cortex with the classical slow progress and recovery first observed by Leao after noxious stimulation of the exposed cerebral cortex of a rabbit (1). The rate of spread (3-6 mm/min) is very characteristic. Also characteristic is the loss of normal response to high CO<sub>2</sub>, whereas normal response to changes in blood pressure are preserved (2). Illustration after Silberstein et al 2002 (3).

1. Leao AAP. Spreading depression of activity in cerebral cortex. *J Neurophysiol*. 1944;7:359-390.
2. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain*. 1994;117 (Pt 1):199-210.
3. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. 2nd ed. London, England: Martin Dunitz; 2002.

## MIGRAINE AURA

- Only 15% of patients experience the classical “slow march” of symptoms typified by migraine with aura
- Lashley calculated rate of expansion of his own visual scotoma to be ~ 3 mm/min
- Initial hyperemia followed by oligemia spreads from the occipital cortex at a rate of 2 – 6 mm/min
- Headache usually starts while cerebral blood flow is diminished

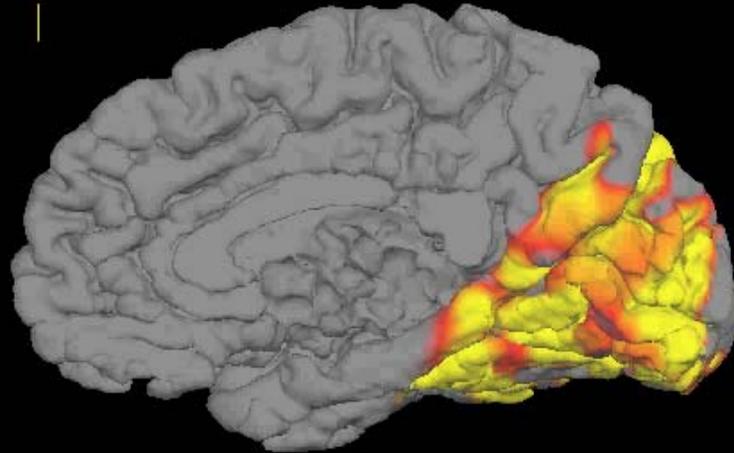
Lashley KS. *Arch Neurol Psych.* 1941. Olesen J et al. *Ann Neurol.* 1990.  
Woods RP. et al. *N Engl J Med.* 1994. Lauritzen M. *Brain.* 1994.

The symptoms of migrainous aura are spectacular and sometimes frightening. Although most migraine patients will never have an aura, much attention has been focused on the phenomenon. The classical, slow progression of symptoms is experienced by only 15%, whereas less specific disturbances cover the whole visual field in about 25% of patients.

Lashley calculated the rate of the characteristic slow march of symptoms to be 3 mm/min (1). This corresponds to the rate of the spreading oligemia that has been observed in studies of cerebral blood flow during aura (2,3). A positron emission tomography (PET) study of spontaneous migraine demonstrated a spreading, bilateral oligemia, which establishes that the phenomenon exists in migraine sufferers (4). It is interesting that headache starts when blood flow is still reduced (3), making it unlikely that vasodilatation is a cause of pain.

1. Lashley KS. Patterns of cerebral integration indicated by the scotomas of migraine. *Arch Neurol Psych.* 1941;46:331-339.
2. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain.* 1994;117(Pt 1):199-210.
3. Olesen J, Friberg L, Olsen TS, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. *Ann Neurol.* 1990;28(6):791-798.
4. Woods RP, Iacoboni M, Mazziotta JC. Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. *N Engl J Med.* 1994;331(25):1689-1692.

## MIGRAINE AURA IS NEURONAL



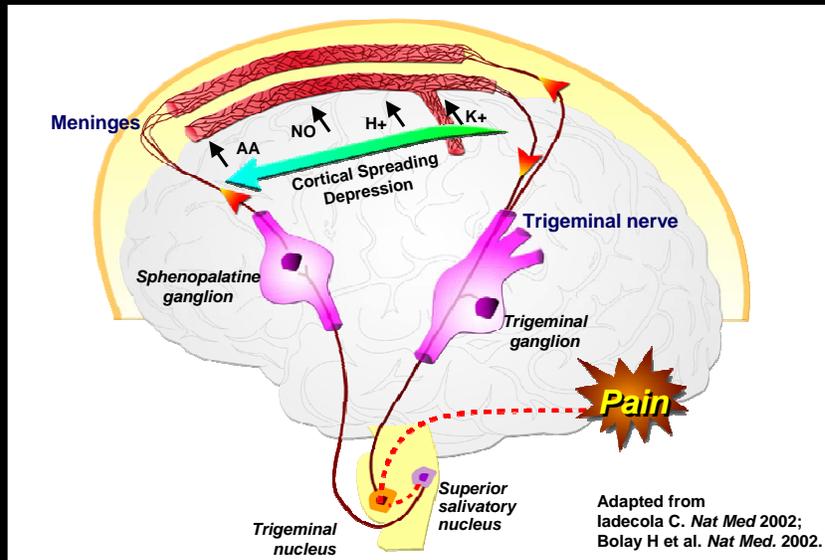
Hadjikhani N et al. *Proc Natl Acad Sci USA*. 2001.

Hadjikhani and colleagues (1) were able to record induced and spontaneous migraine aura. They conclude that migraine aura is not evoked by ischemia. More likely, it is evoked by aberrant firing of neurons and related cellular elements characteristic of cortical spreading depression. Vascular changes follow changes in neuronal activity during the visual aura. It may be that in patients who experience the aura, the neurophysiological events which result in the visual or sensory symptoms also result in activation of trigeminal/cervical nociceptive neurons. Future studies using similar techniques should clarify the correlation of the onset of the headache pain to better understand the relationship between cortical spreading depression and pain.

Shown is the entire hemisphere, from a posterior-medial view. The aura-related changes appeared first in extrastriate cortex. The spread of the aura began and was most systematic in the representation of the lower visual field, becoming less regular as it progressed into the representation of the upper visual field.

1. Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci USA*. 2001;98(8):4687-4692.

## IN PATIENTS WITH AURA, EVENTS INTRINSIC TO CORTEX MAY CAUSE ACTIVATION OF PRIMARY AFFERENT NEURONS



The trigeminal nerve, which innervates the meninges, is intricately involved in migraine. How the migraine is triggered and the cascade of events following the original activation of migraine are not completely understood. However, there is increasing evidence that events intrinsic to the cerebral cortex are capable of affecting the pain sensitive dural vascular structures. If this is the case, then this might explain on way in which the headache is activated in individuals experiencing the aura.

Bolay and colleagues report that, in animal models of migraine, there is a connection between cortical spreading depression (CSD) and activation of trigeminal nerve afferents. Activation of the trigeminal nerve evokes a series of meningeal and brainstem events that appear to be consistent with what is seen during a migraine attack.

Specifically, triggering CSD leads to a long-lasting blood flow increase within the middle meningeal artery. This increase in blood flow is dependent upon trigeminal and parasympathetic activation. In addition, plasma protein leakage occurs in the dura. This is the first study to specifically demonstrate that vasodilation during headache is possibly linked to a series of neurometabolic brain events, including transmission of pain via the trigeminal nerve.

Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med.* 2002;8(2):136-142.

Iadecola C. From CSD to headache: a long and winding road. *Nat Med.* 2002;8(2):110-112.

# MIGRAINE PATHOPHYSIOLOGY

- Genetic basis

- Sensitive brain

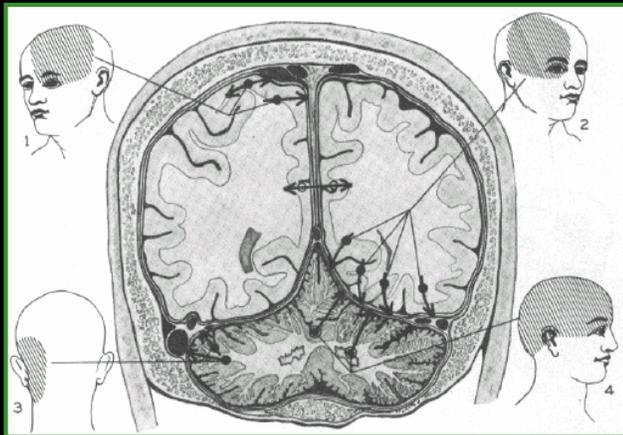
- Triggering migraine

- Migraine aura

- Migraine pain***

Migraine pain and the features of the acute attack have come under intense scrutiny in the last decade. Our enhanced understanding of the disease has been greatly facilitated by the development of new, specific, more effective, acute antimigraine treatments.

## PAIN-PRODUCING INTRACRANIAL STRUCTURES



Ray BS, Wolff HG. *Arch Surg.* 1940.

The vascular theory of migraine pathogenesis that dominated thought in the middle of the 20th century was based on three important observations: 1. The most important structures that register pain in the head are the large cranial vessels, proximal cerebral vessels and dural arteries and the large veins and venous sinuses. These were identified by Ray and Wolff during neurosurgery on awake patients using local anesthesia. 2. The longstanding observation that extracranial branches of the carotid artery became engorged and pulsated during migraine attacks and 3. The most effective antimigraine drug, ergotamine was a potent vasoconstrictor.

Ray BS, Wolff HG. Experimental studies on headache. Pain sensitive structures of the head and their significance in headache. *Arch Surg.* 1940;41:813-856.

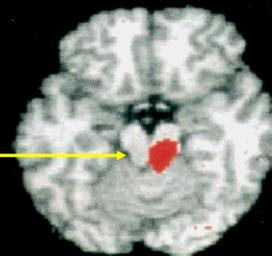
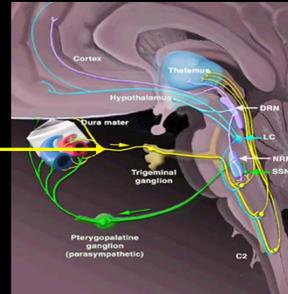
Goadsby PJ. Pathophysiology of headache. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache and Other Head Pain.* 7th ed. New York, NY: Oxford University Press; 2001:57-72.

# MIGRAINE HEADACHE: HOW IS IT GENERATED?

Involves abnormal activation of trigeminocervical afferents

OR

abnormal modulation of trigeminocervical neurons



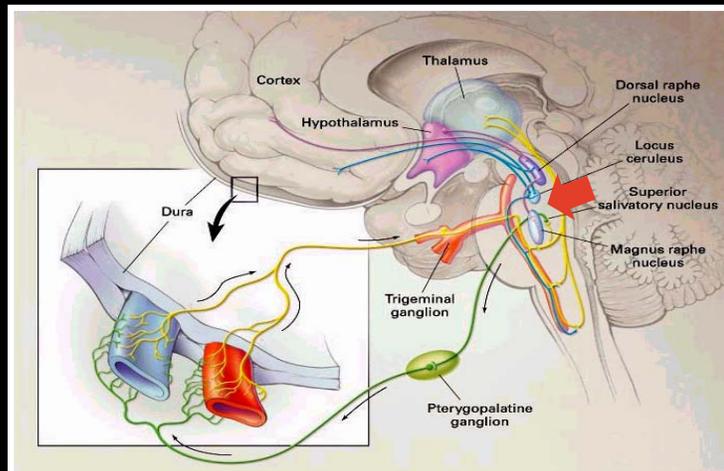
Weiller C et al. *Nat Med.* 1995.

Our understanding of how the headache of migraine is initiated is a work in progress. There is evidence of inappropriate activation of both primary afferent neurons and higher order neurons within the pain modulatory system. Any event that activates the system is capable of causing a headache.

There is a report that supports a completely centrally driven activation. It has been recognized for some time that certain aminergic brainstem nuclei, nucleus locus coeruleus, and dorsal raphe nucleus can alter brain blood flow and are involved in nociceptive control, as well as other modulation of other sensory modalities (1). Raskin and colleagues' clinical observation that placing an electrode into the region of the periaqueductal grey matter can evoke a migraine-like headache (2) reinforced experimental animal findings that stimulation of the locus coeruleus reduces blood flow in a frequency-dependent manner (3). These findings allowed the development of the central neural hypothesis of migraine (4)(5).

1. Goadsby PJ, Lance JW. Brainstem effects on intra- and extracerebral circulations. Relation to migraine and cluster headache. In: Olesen J, Edvinsson L, eds. *Basic Mechanisms of Headache*. Amsterdam, The Netherlands: Elsevier Science Publishers; 1988:413-427.
2. Raskin NH, Hosobuchi Y, Lamb S. Headache may arise from perturbation of brain. *Headache*. 1987;27(8):416-420.
3. Goadsby PJ, Lambert GA, Lance JW. Differential effects on the internal and external carotid circulation of the monkey evoked by locus coeruleus stimulation. *Brain Res*. 1982;249(2):247-254.
4. Goadsby PJ, Zagami AS, Lambert GA. Neural processing of craniovascular pain: a synthesis of the central structures involved in migraine. *Headache*. 1991;31(6):365-371.
5. Weiller C, May A, Limmroth V, et al. Brainstem activation in spontaneous human migraine attacks. *Nat Med*. 1995;1(7):658-660.

# THE NEUROVASCULAR THEORY



Goadsby PJ et al. *N Engl J Med.* 2002.

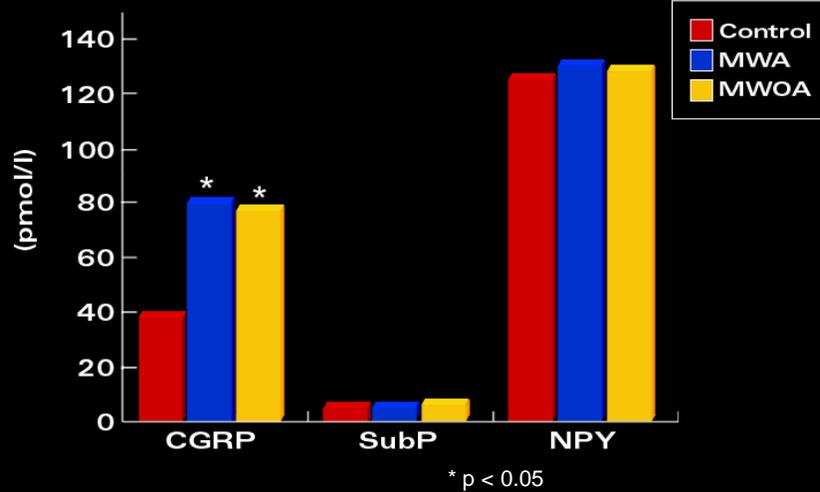
Migraine is a primary brain disorder most likely involving an ion channel in the aminergic brain stem nuclei (←), a form of neurovascular headache in which neural events result in dilation of blood vessels aggravating the pain and resulting in further nerve activation. It involves dysfunction of brain-stem pathways that normally modulate sensory input. The key pathway for the pain is the trigeminovascular input from the meningeal vessels. These nerves pass through the trigeminal ganglion and synapses on second-order neurons in the trigeminothalamic complex, which then project through the quintothalamic tract and, after decussating in the brain stem, form synapses with neurons in the thalamus.

A reflex connection exists between neurons in the pons in the superior salivatory nucleus, which results in a cranial parasympathetic outflow that is mediated through the pterygopalatine, otic, and carotid ganglia. This trigeminal-autonomic reflex is present in normal persons but is expressed most strongly in patients with trigeminal-autonomic cephalgias, such as cluster headache and paroxysmal hemicrania. It may also be active in migraine.

Brain imaging studies suggest that important modulation of the trigeminovascular nociceptive input stems from dorsal midbrain, periaqueductal grey and the dorsal raphe nucleus, and the pons, the locus coeruleus.

Goadsby, PJ, Lipton RB, Ferrari, MD. Migraine. Current Understanding and Treatment. *N Engl J Med* 2002;346:257-270. Copyright (C) 2002. Massachusetts Medical Society. All rights reserved.

## TRIGEMINAL NEUROPEPTIDES RELEASED DURING MIGRAINE ATTACKS



Goadsby PJ et al. *Ann Neurol.* 1990.

This diagram illustrates the elevation of calcitonin-gene-related peptide (CGRP), but not substance P, in the external jugular venous blood of patients with acute migraine with aura (MWA) and migraine without aura (MWOA) (1). In animal studies SP, NKA and CGRP are all increased with stimulation of the trigeminal ganglion.

1. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol.* 1990;28:183-187.

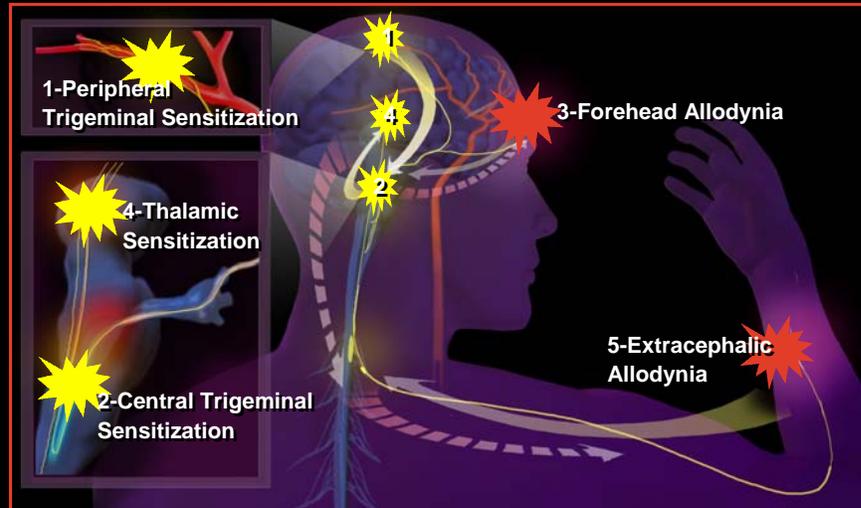
## PERIPHERAL PROCESSING: STERILE NEUROGENIC INFLAMMATION

Cutrer FM et al. *Headache: Bluebooks of Practical Neurology*. 1997.

This diagram from Cutrer and colleagues illustrates the neurally-induced plasma protein extravasation model of trigeminal activation.

Cutrer FM, Limmroth V, Woeber C, et al. New targets for antimigraine drug development. In: Goadsby PJ, Silberstein SD, eds. *Headache: Bluebooks of Practical Neurology*. Vol. 17. Philadelphia, PA: Butterworth-Heinemann; 1997:59-120.

## CENTRAL PROCESSING: CUTANEOUS ALLODYNIA



Burstein R et al. *Brain*. 2000.

Most migraine patients exhibit cutaneous allodynia inside and outside their pain-referred areas during migraine attacks. Burstein and colleagues studied the development of cutaneous allodynia in migraine by measuring the pain thresholds in the head and forearms of a patient at several points during the migraine attack (1, 2, and 4 hours after onset) and compared the pain thresholds in the absence of an attack. This study demonstrated that a few minutes after the initial activation of the patient's peripheral nociceptors, these became sensitized and mediated the symptoms of cranial hypersensitivity. The barrage of impulses then activated second-order neurons and initiated their sensitization, mediating the development of cutaneous allodynia on the ipsilateral head. The sensitized second-order neurons activated and eventually sensitized third-order neurons leading to allodynia on the patients contralateral head and forearms by the two-hour point, a full hour after the initial allodynia on the ipsilateral head.

The authors concluded that this progression of symptoms calls for the early use of antimigraine drugs that target peripheral nociceptors before central sensitization occurs.

Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack: clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain*. 2000;123 (Pt 8):1703-1709.

## CENTRAL SENSITIZATION: *OCCURS SEQUENTIALLY OVER TIME*

In a spontaneous case of migraine with aura

- Allodynia not present interictally
- Appeared in Ipsilateral face at 1 hour
- Appeared Contralateral face and Ipsilateral arm at 2 hours
- Intensified in similar distribution at 4 hours

This has therapeutic significance, implying sensitization above the TNC and a mechanistic rationale for early treatment

In a spontaneous case of migraine with aura the evolution of changes in detail sensory testing was followed over time.

Allodynia not present interictally

Appeared in Ipsilateral face at 1 hour

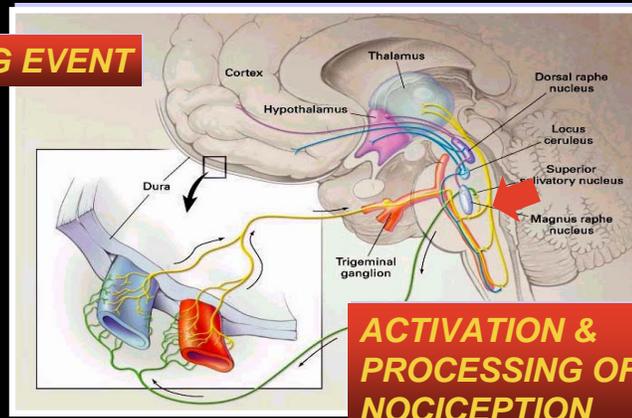
Appeared Contralateral face and Ipsilateral arm at 2 hours

Intensified in similar distribution at 4 hours

This has therapeutic significance, implying sensitization above the TNC and a mechanistic rationale for early treatment

# MIGRAINE PATHOPHYSIOLOGY: OVERVIEW

## INITIATING EVENT



## ACTIVATION & PROCESSING OF NOCICEPTION

**Both Provide Targets for Therapeutic Intervention**

Goadsby PJ et al. *N Engl J Med*. 2002.

Migraine is a complex primary brain disorder that involves a cascade of events that lead to recurrent inappropriate activations of the trigeminocervical pain system. The initiating events are currently the focus of study and may prove to be invaluable targets for future prophylactic treatments. The events involved in activation and processing of the nociceptive depolarization within the trigeminocervical pain system may provide therapeutic targets for acute and preventative treatments.

Goadsby, PJ, Lipton RB, Ferrari, MD. Migraine. Current Understanding and Treatment. *N Engl J Med* 2002;346:257-270. Copyright (C) 2002. Massachusetts Medical Society. All rights reserved.

## MIGRAINE PATHOPHYSIOLOGY: CONCLUSIONS

*Migraine is a neurovascular headache*

- Migraine has a significant genetic component
- The biology of migraine is increasingly well understood
- Treatment of migraine can be optimized and understood in terms of the anatomy and physiology of the condition

In conclusion, we have seen that migraine is a neurovascular headache. A significant genetic component to predisposition to migraine exists, and the functional consequences of the genetics are beginning to be explored. The biology of migraine is better although not completely understood. This increased understanding provide great opportunities to continue to improve treatment.