Migraine Diagosis and Pathophysiology

손 종 희
한림대학교 의과대학 신경과학교실

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- Migraine Attack Initiation (prodrome / aura)
- Migraine Attack Activation & Evolution (pain mechanism)
- Vulnerability to Migraine

Diagnosis of Migraine : Migraine without aura

Diagnostic criteria for migraine without aura (ICHD-3 beta)

A.	At least five attacks fulfilling to criteria B to D.
B.	Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated).
C.	Headaches has at least two of the following 4 characteristics:
	1- unilateral location
	2- pulsating quality
	3- moderate or severe pain intensity
	4- aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs).
D.	During headache at least one of the following:
	1- nausea and/or vomiting
	2- photophobia and phonophobia.
E.	Not better accounted for by an order ICHD-3 diagnosis

Diagnosis of Migraine : Migraine with aura

Diagnostic criteria for migraine with aura (ICHD-3 beta)

A. At least two attacks responding to criteria B and C.

B. B. One or more of the following fully reversible aura symptoms:

- 1- visual
- 2- sensory
- 3- speech and/or language
- 4- motor
- 5- brainstem
- 6- retinal

C. At least two of the following four characteristics:

- 1- at least one aura symptom spreads gradually over ≥ 5 minutes, and/or 2 or more symptoms occur in succession
- 2- each individual aura symptom last 5–60 minutes
- 3- at least one aura symptom is unilateral
- 4- the aura is accompanied, or followed within 60 minutes by headache

D. Not better accounted for by an order ICHD-3 diagnosis, and transient ischemic attack has been excluded

Migraine with typical aura

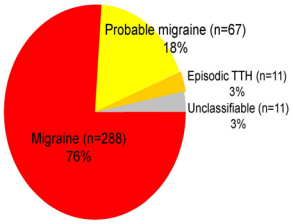
Hemiplegic migraine

Migraine with brainstem aura

Retinal migraine

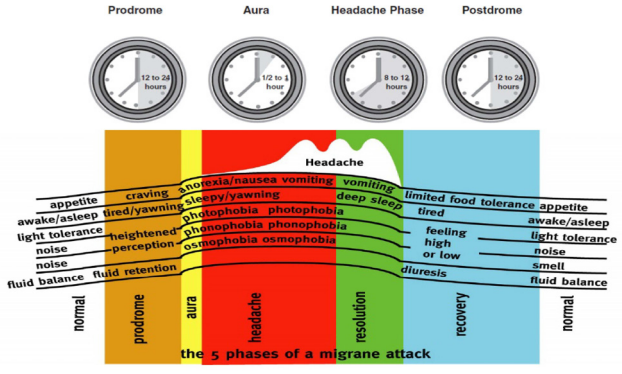
Migraine is under-diagnosed

- A critical analysis of IHS diagnostic criteria shows acceptable inter-observer variability, good specificity, but poor sensitivity
- Landmark study (2004) : In a prospective, open-label study of 1203 patients with episodic headache



- 94% of patients presenting to a primary physician with recurrent headache met IHS criteria for migraine or probable migraine
- 25% of migraine patients did not receive a diagnosis of migraine

Description of the migraine attack



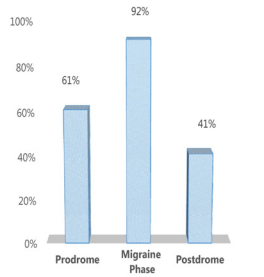
Migraines are often misdiagnosed

- Other symptoms : mood change, fatigue, yawning, neck stiffness, polyuria, gastrointestinal disturbances, and variety of visual, somatic sensory, and cognitive phenomenon
- Visual aura : only 15-20% of migraineurs
- Head pain can be non-throbbing : in ~40% of patients,
  can be bilateral : in ~ 43% of patients
- Sinus pain and pressure, stuffiness, rhinorrhea & weather association is often present
  - in up to 97% of migraine attacks
- Neck pain is often present
  - in up to 75% of migraine attacks

Neck Pain During Migraine

- Prevalence
  - 75% of subjects
- Descriptions
  - 69% - tightness
  - 17% - stiffness
  - 5% - throbbing
  - 5% - other

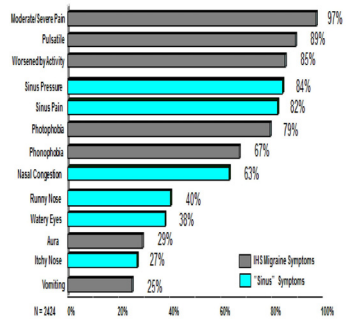
Percentage of patients who met IHS criteria for migraine reporting neck pain during the prodrome, headache phase, or postdrome of their migraine attacks



(Kaniecki R, *Neurology*, 2002)

Sinus Symptoms During Migraine

"Sinus symptom" are common in the presentation of migraine

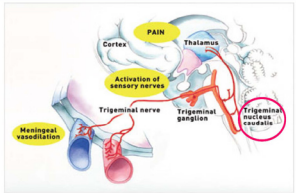


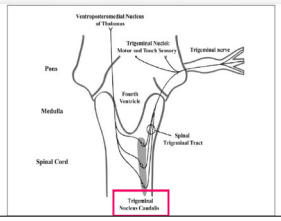
(Schreiber C. *AHS meeting*, 2002)

- 45% of migraine patients report sinus symptoms including lacrimation, nasal congestion and rhinorrhea
- Many migraine suffers have significant sinus symptoms ->misdiagnose migraine headache as 'sinus' headache

Anatomy of Head Pain I

- The trigeminovascular system consists of the trigeminal nerve and its peripheral and central connections.
- Peripherally, it innervates the meninges, intracranial venous sinuses and proximal portions of cerebral arteries, extracranial blood vessels, the face and contents of the anterior oropharinx, nasal sinuses and orbits.
- Centrally, it connects with the trigemino nucleus caudalis,(connection to upper cervical segments) which run to thalamus and to somatosensory cortex.

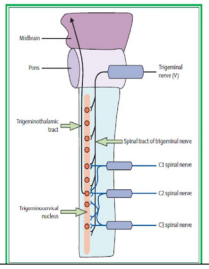




Anatomy of Head Pain II

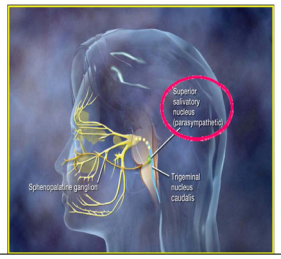
- Trigeminovascular system linking the fifth cranial nerve territory and the upper cervical regions via the trigeminal nucleus caudalis (TNC)

->explains referred pain between face and the neck

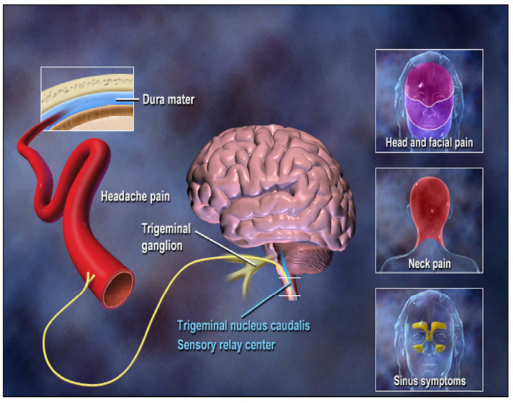


- Polysynaptic connections between the TNC and the parasympathetic superior salivatory nucleus in the pons

->explain the 'sinus' symptoms in migraine suffers and ipisilateral autonomic phenomenon during headache attack



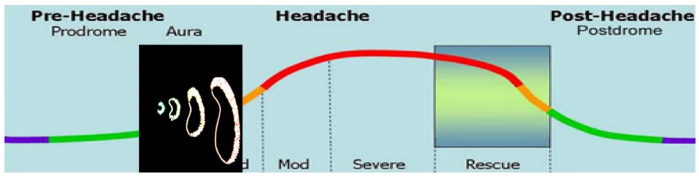
One Nerve Pathway: Multiple Symptoms of Migraine



Pathophysiology of Migraine

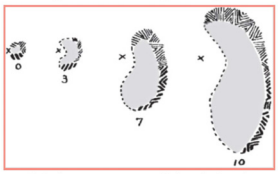
- **Migraine Attack Initiation** (prodrome / aura)
  - Cortical spreading depression vs Brainstem activation
- **Headache Activation & Evolution** (pain mechanism)
  - Trigeminovascular activation & Neurogenic inflammation
  - Peripheral & Central sensitization
- **Vulnerability of Migraine**
  - Migraine is an inherited CNS disorder
  - Migraineurs have excitable brain

Initiation of Migraine Attack



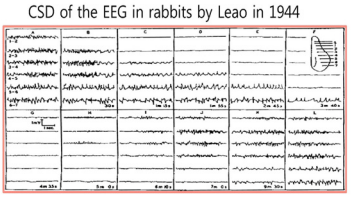
Cortical spreading depression

Drawing of visual aura by Lashley in 1941



occipital cortex as an origin of visual aura 3mm/min speed for migraine nature of symptom

CSD of the EEG in rabbits by Leao in 1944



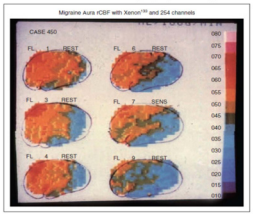
wave of neuronal excitation followed by neuronal depression which moves across the cerebral cortex at rate of about 3mm/min

- Similarity between the velocity of CSD propagation and the march of visual aura reported by Lashley
- Cortical spreading depression (CSD) may be related to migraine with aura

  Similar phenomenon in humans have been imaged in humans using PET and fMRI

Neuroimaging in Cortical Spreading Depression

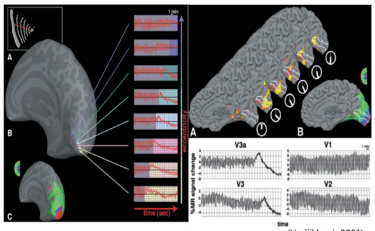
Intra-arterial ^{133}Xe tomography during aura



(Olesen , 1981)

- slowly spreading oligemia was found
- propagating anteriorly from the occipital cortex with a speed similar to that of CSD

Brain oxygen level-dependent (BOLD) imaging



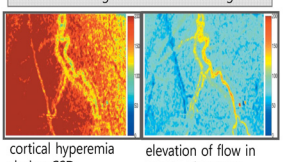
(Hadjikhani, 2001)

- Focal increase in BOLD signal was detected during visual aura, spreading within occipital cortex at a rate of 3 mm/min
- Initial BOLD increase was followed minutes later by a decrease, suggesting a rise and then a fall in CBF

CSD active trigeminal nociceptive pathways

- CSD was able to induce trigeminovascular activation and neurogenic edema that is characteristics feature of headache phase

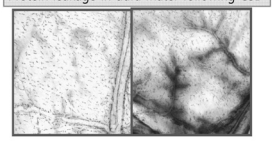
Blood-flow images of MMA following CSD



cortical hyperemia during CSD

elevation of flow in MMA after CSD

Protein leakage in dura mater following CSD



normal

following CSD

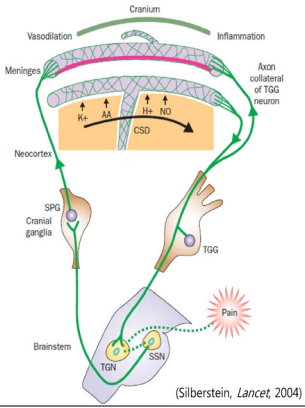
- CSD activates ipisilateral trigeminal nucleus caudalis

Table 1 C-fos-positive cells in trigeminal nucleus caudalis (lamina I, IIo) following repetitive unilateral CSD

Brainstem below Obex (mm)	Sham (n=9) R	Sham (n=9) L	NCNT (n=6) R	NCNT (n=6) L	Sumatriptan (n=4) R	Sumatriptan (n=4) L
0—1.0	21 ± 1	17 ± 2	17 ± 1	18 ± 1	15 ± 2	13 ± 1
1.0—3.0	59 ± 3*	48 ± 4	49 ± 4	42 ± 4	58 ± 4	50 ± 3
3.0—6.0	81 ± 4	62 ± 4	54 ± 3	52 ± 2	70 ± 6	67 ± 5

(Bolay, *Nat Med*, 2002)

The relation between CSD and headache in migraine with aura



(Silberstein, *Lancet*, 2004)

- CSD can be a migraine trigger
- CSD occurs in the cerebral cortex, cerebellum, and hippocampus
- As the wave of depolarization moves across the cerebral cortex,

->vasoactive & noxious substances (NO, arachidonic acid, protons, potassium) accumulate in the extracellular space

matrix metalloprotease is activated, which affect the blood brain barrier

->trigger perivascular trigeminal nociceptors

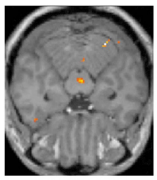
->activation of the trigeminal nucleus in the brainstem

->project to both sensorial & limbic cortex via thalamus

Brainstem Activation in Migraine

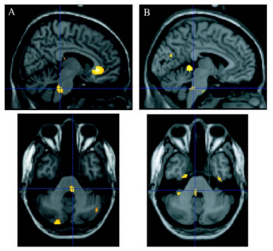
- Brainstem aminergic nuclei can modify trigeminal pain processing
- PET demonstrates brainstem activation in spontaneous migraine attacks

Brainstem activation during acute migraine



- Increased rCBF in the dorsal rostral brainstem persisted even 30 min after pain relief following treatment with sumatriptan (Bahra A et al, *Lancet* 2001)

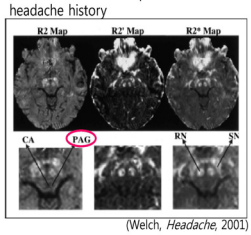
Activation of the ipsilateral pons in patients with unilateral pain



(Afridi, S. K. et al. *Brain* 2005)

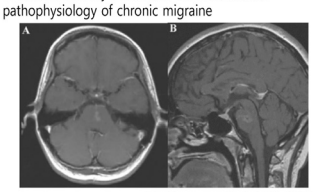
Brainstem generator? vs modulator?

Iron deposition in the PAG : Degree of PAG structural alteration depends on duration of headache history



(Welch, *Headache*, 2001)

Symptomatic migraine and pontine vascular malformation: evidence for a key role of the brainstem in the pathophysiology of chronic migraine



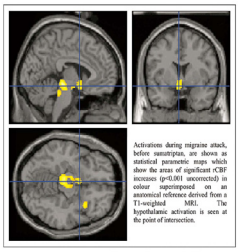
(M Obermann, *Cephalalgia*, 2006)

- Placement of electrodes in PAG for treatment of chronic pain->migraine-like headache in non-migraineur
- Stimulation of the locus coeruleus can evoke reductions in the cerebral blood flow, raising the possibility that a process beginning in the brainstem could generate cortical hypoperfusion associated with migraine attacks (Goadsby PJ et al. *Brain Res.* 1989)

Hypothalamic activation in Migraine

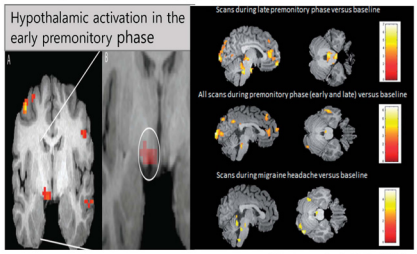
- Premonitory phase of migraine involves changes in the activity of the hypothalamus

Increased blood flow in the hypothalamus during a spontaneous migraine attack



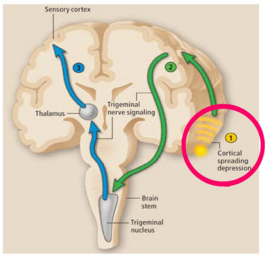
(Denuelle et al. *Headache*. 2007)

Increased hypothalamic blood flow correlated with migraine premonitory symptoms

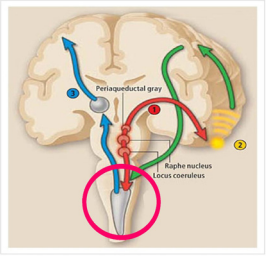


(Sprenger et al. *Brain*. 2014)

Migraine "generator" theories



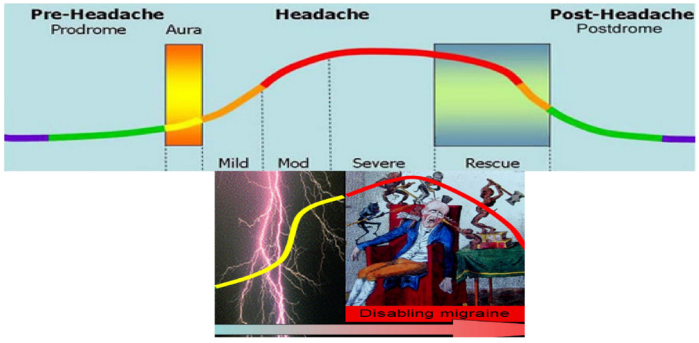
VS



- CSD (in migraine with aura) causes the migraine to begin
- A "silent" CSD (in migraine without aura) give rise to migraine attack

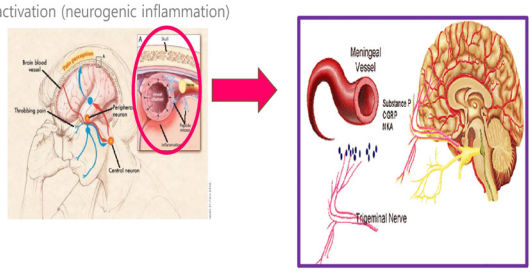
- Migraine triggers activate brainstem structure (dorsal raphe nucleus, periaqueductal grey, locus coeruleus) and begin the migraine attack

Activation & Evolution of Migraine Attack



Neurogenic inflammation

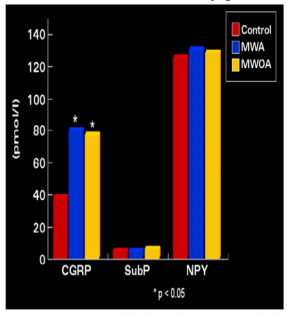
- Trigeminal neurons supplying the dural vessels release calcitonin gene-related peptide(CGRP), substance P, and neurokinin A
- The vessel dilate and become inflamed, plasma protein extravasation occurs and mast cell degranulation, activation (neurogenic inflammation)



CGRP (Calcitonin Gene Related Peptide) in Migraine

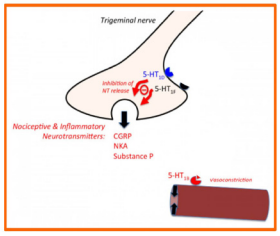
- CGRP=main neuropeptide that is released by acivated trigeminovascular afferents during migraine, potent vasodilator
- Increased CGRP is found in the jugular veins of patients with migraines during an attack
- CGRP infusion evokes migraine
- CGRP receptor antagonists effectively abort a migraine attack

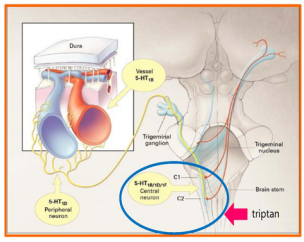
Elevation of CGRP in the external jugular vein



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

5-HT receptors in the trigeminovascular system



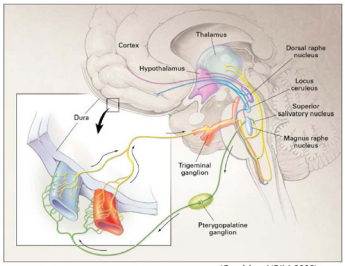


- $5\text{-HT}_{1D/1F}$ receptors-peripheral trigeminal n. endings
  : Inhibit perivascular neuropeptide release
- 5-HT_{1B} receptors-blood vessels
  : Vasoconstriction

- $5\text{-HT}_{1B/1D/1F}$ receptors-CNS
  : Inhibit the release of 5-HT, noradrenaline and acetylcholine
  ->interrupt pain transmission within brain

Trigeminovascular Mechanism

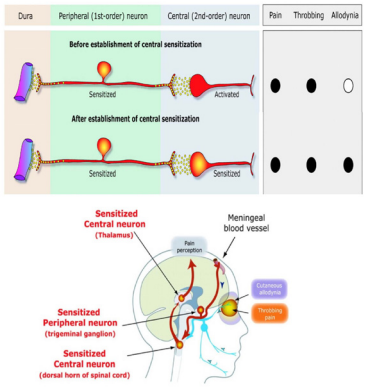
- The key pathways for the pain are the trigeminovascular input from the meningeal vessel, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex~project through the quintothalamic tract, and after decussation in the brainstem, from synapses with neurons in the thalamus



(Goadsby, *NEJM*, 2002)

- There are reflex connection between neurons in the pons in the superior salivatory nucleus, which result in a cranial parasympathetic outflow that is mediated through the pterygopalatine, otic and carotid ganglia.
- This trigemino-autonomic reflex is present in normal persons and regulation may be abnormal in migraine attacks

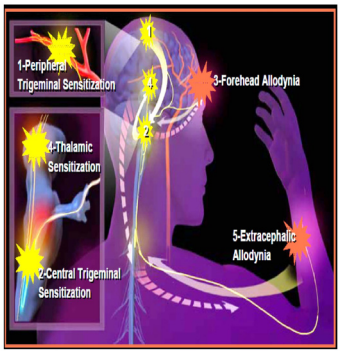
How does the headache persist and intensify long after the inciting activation has passed?



- Vasodilatation, mast cell activation, mechanical disruption->contribution to the sensitization of the trigeminal primary afferent neurons (peripheral sensitization)
- If attack progresses further, second-and third-order neurons may be activated (trigemino-thalamic and thalamocortical)

(central sensitization, wind-up)

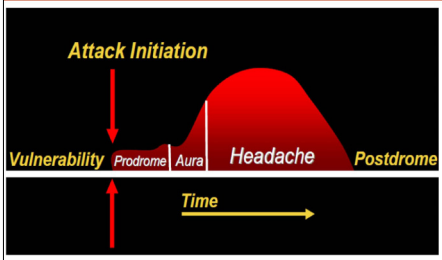
Central Sensitization: Cutaneous Allodynia

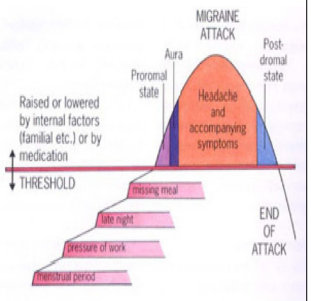


(Burstein R et al. *Brain.* 2000)

- 80% of patients with migraine had cutaneous allodynia during attacks
- Allodynia in ipisilateral face at 1 hour (2nd order neuron activation)
- Allodynia in contralateral face and ipisilateral arm at 2 hours (3rd order neuron activation)
- This has therapeutic significance, implying sensitization above the TNC and a mechanistic rationale for early treatment

Vulnerability to migraine

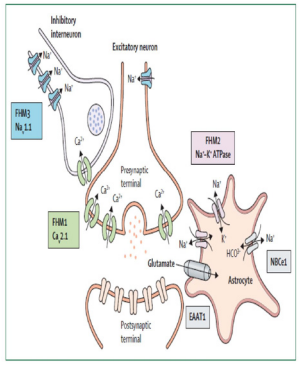




Genetic basis I

- Twin studies : MZ > DZ
- Ion channelopathy : Familial hemiplegic migraine

Type	Gene Involved	Chromosome	Channel Subunit Encoded	Percentage of Families Linked
FHM1	*CACNA1A*	19p13	α1 subunit of $Ca_v2.1$ (P/Q type)	~50–75%
FHM2	*ATP1A2*	1q23	A1A2 Na^+/K^+-ATPase	~10–30%
FHM3	*SCN1A*	2q24	α1 subunit of $Na_v1.1$	Unknown



Genetic basis II

- Mutation in glutamate transporter EAAT1 (excitatory amino acid transporter)

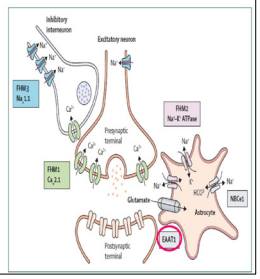
: reduced capacity for glutamate reuptake->increase hyperexcitability

associated with episodic ataxia, seizure and hemiplegic migraine

- Low magnesium levels in patients with migraine

: Mg^{++}-inhibitory ion, blocking calcium channels

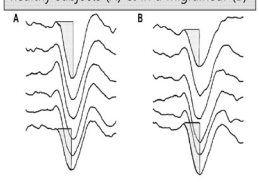
- The results of genetic alterations is a hyperexcitable brain



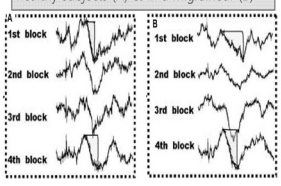
Hyperexcitable Brain in Migraine

- Migraine patients have been described as having a hyperexcitable brain, being sensitive to environmental triggers and being unable to habituate to repetitive stimuli
- Evoked potential studies showed a lack of habituation to repetitive stimuli

Visual evoked potentials habituation in a healthy subjects (A) & in a migraineur (B)



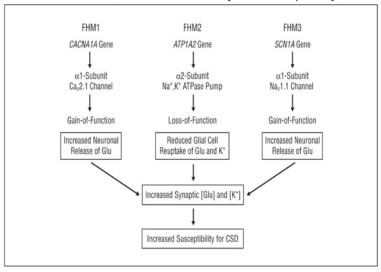
Auditory evoked potentials habituation in a healthy subjects (A) & in a migraineur (B)



- Habituation deficit in migraine indicates an abnormal excitability of the cerebral cortex

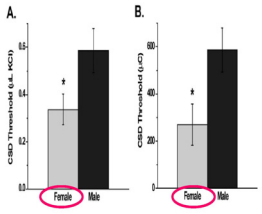
Genetic & Hormonal factors modulated migraine susceptibility

Schematic representation of the mechanism by which FHM genes can cause increased neuronal excitability and susceptibility to CSD



(Rob C, *Arch Neurol*, 2007)

Reduced threshold for activation of CSD in female vs male mice

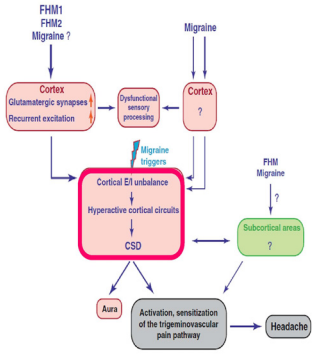


(Brennan, *Ann Neurol*, 2007)

Hyperexcitable Brain in Migraine

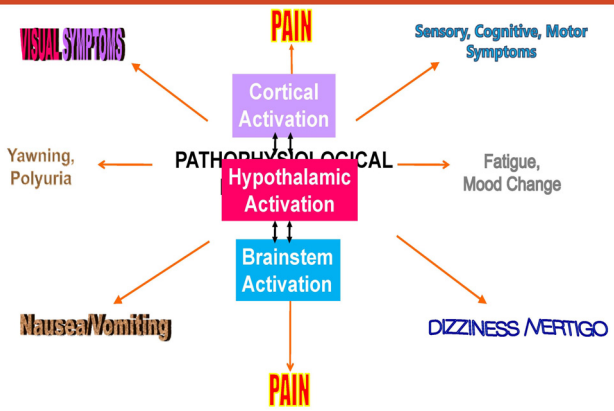
Excessive excitation (cortical hyperexcitability)

- Due to abnormal release of excitatory neurotransmitter
  - -higher plasma concentration of glutamate in migraineurs
  - -alterations in Ca^{2+} channel function produced by FHM mutation
- Due to reduced intracortical inhibition
  - -low brain Mg^{2+}
  - -altered brain energy metabolism

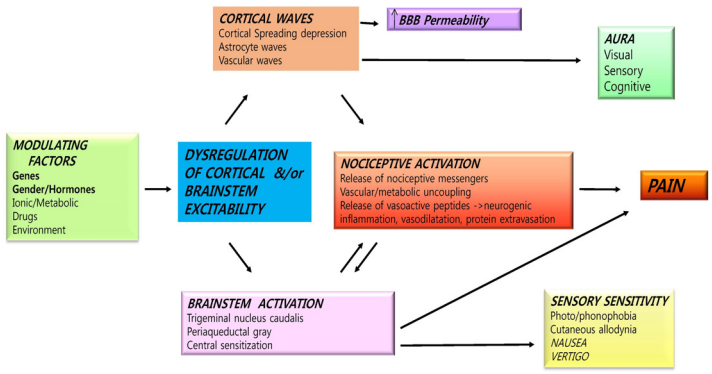


(Pietrobon, *Trends in Neuroscience*, 2012)

Migraine- multisymptom complex



Hypothesized Sequence of Events in Migraine



Summary

- Migraine is a common clinical disorder that is generally hereditary.
- Migraine as a disorder of brain excitability characterized by deficient regulation of the cortical excitatory-inhibitory balance, and their relationship to CSD susceptibility.
- Activation of trigeminovascular system, leading to vasodilation and neurogenic inflammation of meningeal blood vessel and thus, throbbing pain. (Inflammatory neuropeptides, particularly CGRP are involved)
- As an acute attack progresses, second-and third-order neurons are involved, resulting in central sensitization may occur with cutaneous allodynia