# Pathophysiology of Migraine

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Migraine is a complex neurologic disorder characterized by:

1. Recurrent episodes of headache

2. Other associated symptoms

3. Neurologic dysfunction in the period between attacks of migraine headache (interictal phase)

# Moving away from *vascular hypothesis* for migraine

The early vascular theory is not supported by available evidence:

Vasoconstriction as the mechanism of the migraine aura and vasodilation as the mechanism of migraine pain ×

- MRA studies have shown that changes in the caliber of extra/intracranial vessels are neither necessary nor sufficient to cause migraine pain. It is likely that vascular changes are a reflection of activity in the brain and in perivascular nerves.

- The throbbing quality was presumed to be a reflection of aberrant sensitivity to vascular pulsation:
  - ✓ The throb rate of migraine is significantly slower than arterial pulse.
  - ✓ The throb nature could be a reflection of slow oscillations in cellular activity in the thalamus or brainstem.

In order to frame the discussion of the pathophysiology of migraine (Neurophysiological/molecular):

In general, five phases are recognized:

- Prodromal or premonitory/preictal
- Aura
- Headache
- Postdrome/postictal
- Interictal

These phases may overlap or may not occur consistently from attack to attack

# PRODROMAL (PREMONITORY) PHASE

- In around 80% of people with migraine, 48 hours preceding the headache
- Hypothalamic activation (posterolateral hypothalamus): polyuria, yawning, food cravings, and changes in appetite and alterations in homeostasis
- The locus coeruleus: sleep disturbances
- Activation in the rostral dorsal medulla and periaqueductal gray is associated with nausea (the role of the brainstem in the initiation of a migraine attack)
- Neck discomfort, often present during the prodromal phase, is due to activation of the trigeminocervical complex

# PRODROMAL (PREMONITORY) PHASE

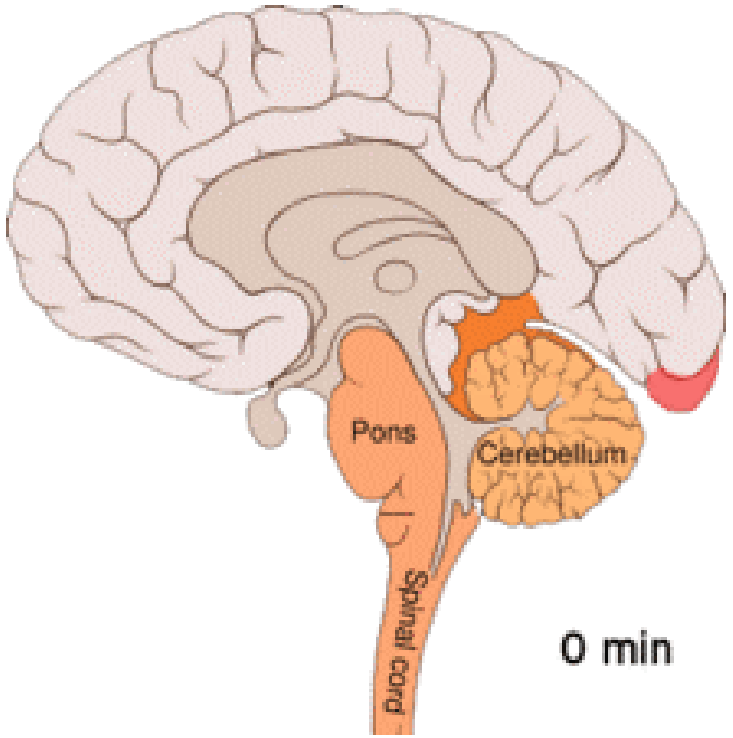
- Activation of the visual cortex: Photic hypersensitivity
- Photophobia/Phonophobia/Osmophobia: Reduced habituation :

  Repeated stimulation does not result in decrement in response

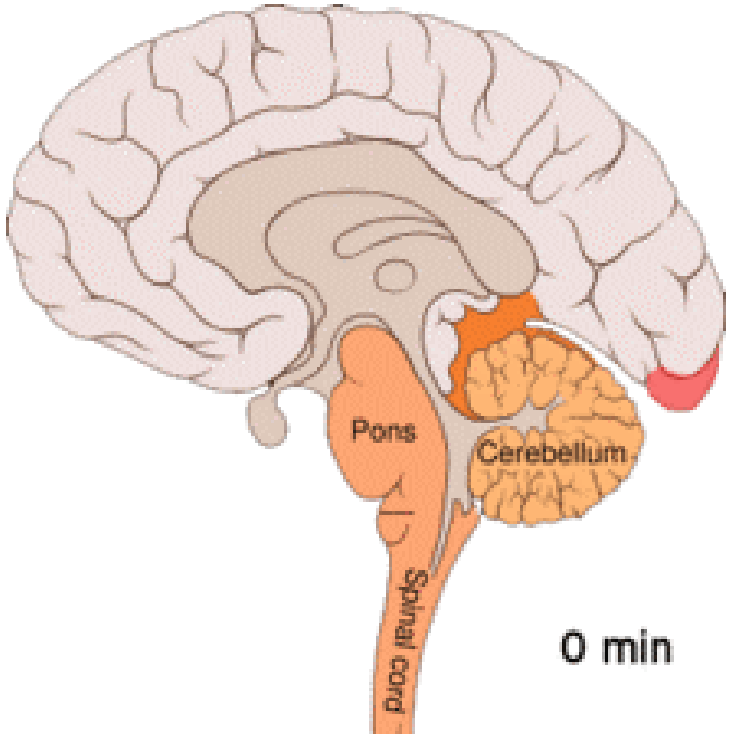
- Increased sensory sensitivity reflects ‘central sensitization’, i.e. changes in sensory processing
- The early occurrence of sensory sensitivity before pain indicates that central sensitization is a primary event rather than a secondary consequence of painful input from the peripheral nervous system.

# AURA PHASE

- About 30– 40% of migraineurs experience at least two auras in their life.
- It consists of visual, sensory, motor, language, or brainstem disturbances.
- Pain and associated symptoms of migraine may occur in parallel with aura, rather than as a direct downstream consequence of the aura phenomenon. It is also not rare to occur in the absence of headache.
- Pathophysiologic mechanism of the aura is cortical spreading depression (CSD)
- CSD is a bioelectrical phenomenon consisting of a wave of excitation associated with hyperemia followed by a more prolonged period of inhibition of neural and glial activity associated with cortical oligemia that propagates slow across the brain surface at a velocity of 3-5 mm/min
- Visual aura appear to propagate in a linear fashion along gyri or sulci, rather than spreading as a concentric wave.



- Different cellular pathways, perhaps driven by different genetic variations, could lead to spontaneous increases in K+ and glutamate release
- This can release messengers that generate headache, including NO, ATP, CGRP.
- CSD cause activation of trigeminal nociceptive and brainstem neurons
- Aura can start in multiple sites of the visual cortex
- Aura may propagate silently in the cortex, without clinical manifestations.
- CSD threshold is reduced by:
  - ✓ Gene mutations associated with FHM and familial migraine with
  - ✓ female sex
  - ✓ estrogen (consistent with the significantly higher prevalence of migraine in women)
- Multiple established migraine preventive medications with diverse mechanisms of action have all been reported to inhibit CSD.



# HEADACHE PHASE

The clinical hallmark of a migraine attack is head pain

Migraine pain is mediated by the trigeminovascular pathway:

Some experts maintain that nociceptive activation of the peripheral trigeminal nociceptors is necessary for the perception of head pain

Others argue that migraine pain is the result of abnormal central processing of otherwise normal sensory input from the peripheral trigeminal sensory system.

- Recent studies in humans and rodents have shown that trigeminal meningeal afferents may have extracranial projections, this could be a pathway by which extracranial triggers (and therapies) could modulate intracranial mechanisms of migraine.

- The first three cervical nerves (C1-C3) may be important mediators of primary headaches. Patients commonly report neck pain in different migraine phases.

- Pain input from the C1– C3 nerves converges with input from the trigeminal nerve in the caudal portion of the trigeminal nucleus caudalis in the medulla and cervical spine.

# POSTDROMAL PHASE

- More than 80% of patients report nonheadache symptoms in 24 to 48 hours following resolution of HA
- Research on the postdrome help identify treatments to accelerate the return to normal function.
- The most common postdromal symptoms are :
  - ✓ Being tired or weary, reported in 88%
  - ✓ Difficulty concentrating occurred in more 50%
  - ✓ Stiff neck in 42%
  - ✓ Other symptoms, such as nausea, photo/phonophobia, were also reported but were less frequent
- Acute treatment do not appear to have any effect on the occurrence of the postdrome
- Brain regions and mechanisms responsible for the prodromal phase could also play a role in the postdromal phase.
- Global reductions in CBF could occur in this phase and could be mediated by activation of brainstem nuclei, resulting in widespread vasoconstriction or persistent hypoperfusion that follows the bioelectric phenomenon of CSD.

# Interictal Phase

- Different symptoms can be grouped into:
  - ✓ Sensory hypersensitivity (hypersensitivity to light, sounds, and odors )
  - ✓ Autonomic symptoms (dizziness or a sense of being off balance)
  - ✓ Cognitive dysfunction

Altered network connectivity resulting in **hyperresponsivity and lack of habituation** has been demonstrated in multiple **cortical and subcortical brain regions** during the interictal phase when comparing people with migraine during the interictal phase with healthy nonheadache controls as well as comparing people with migraine during and outside their migraine attacks

# Migraine and MOLECULAR MEDIATORS

- **Calcitonin gene- related peptide(CGRP)**
- Serotonin
- **Dopaminergic mechanisms**
- The orexigenic system
- **Noradrenergic activity**
- Insulin, glucagon, leptin, and neuropeptide Y, Somatostatin, cholecystokinin, antidiuretic hormone, and melatonin
- **Pituitary adenylate cyclase- activating peptide(PACAP)**
- Prostaglandins

# Calcitonin gene- related peptide(CGRP)

- CGRP and its receptors are found in multiple locations in peripheral and central nociceptive
- Recovery of normal vascular caliber after vasoconstriction.
- Levels of CGRP in serum are elevated during spontaneous and NG- evoked migraine attacks.
- Both serum and salivary CGRP levels may be reduced in pain relief by treatment with a triptan.
- IV CGRP causes a delayed migraine attack in, this can be effectively treated with sumatriptan.
- CGRP receptor antagonists and CGRP antibodies are effective as acute and preventive migraine therapies.
- Preventive efficacy of anti- CGRP antibodies, which presumably do not cross the BBB, indicate that 'neutralizing' CGRP peripherally can effectively prevent migraine.

# Serotonin

- Low levels of serotonin in migraine, suggests these reduced CNS serotonin levels could increase the propensity to migraine.

- While the efficacy of triptans, selective agonists of 5- HT1B, D, and F receptors, suggests a role for serotonin in migraine therapy, the lack of efficacy of most SSRIs as migraine preventive therapies argues against low levels of brain serotonin as a primary causative mechanism of migraine.

- The triptans, remain the cornerstone of acute migraine treatment. However, their vasoconstrictive effect represents a hurdle and contraindication for a subset of patients . Recently, a new class of more selective serotonin receptor agonists targeting 5-HT1F receptors, which are absent on blood vessels, has emerged as an alternative to triptans. Lasmiditan, the first drug in this new class named ditans, has recently been approved for acute migraine treatment.

- **Dopaminergic** mechanisms are likely to mediate some of the symptoms of migraine in different phases, more notably yawning, nausea, and difficulty concentrating.

- **The orexigenic system** are implicated in the alterations of sleep and fatigue in migraine. Orexin A and B modulate dural nociception.

- In the locus coeruleus, **noradrenergic activity** plays a role in sleep-wake regulation and arousal as well as pain in migraine.

- Multiple neuroendocrine mediators, such as **insulin, glucagon, leptin, and neuropeptide Y**, have effects on the trigeminovascular system, linking changes in appetite, food cravings, and migraine. Other emergent neurochemical systems that may be implicated in migraine include **somatostatin, cholecystokinin, antidiuretic hormone, and melatonin.**

# Pituitary adenylate cyclase- activating peptide(PACAP)

- PACAP is elevated during spontaneous migraine attacks as compared with between attacks , and systemic administration of PACAP precipitates a delayed migraine attack. In the past decade, PACAP has emerged as a potential therapeutic target for migraine and a significant focus for research

- PACAP and its receptors are expressed in multiple regions believed to be involved in migraine, including the trigeminal ganglion, SPG, TNC, hypothalamus, and thalamus.

- PACAP binds to different receptors,: VIP and PAC1. VIP causes significant cerebral vasodilation but does not consistently cause migraine. PAC1 receptor, which is bound with significantly higher affinity by PACAP compared with VIP, is the receptor primarily involved in PACAP's role in migraine.

# Prostaglandins

- Infusion of either prostaglandin (PG) E2 or I2 evokes a migraine-like headache

- Migraine attack evoked by PGE2 occurred immediately after infusion in the majority of patients, in contrast to the 2– 4- hour delay before the occurrence of migraine that was more commonly observed with PGI2 or with all other reported migraine triggers.

- Elevated levels of PGE2, PGD2, and PGF2α in saliva is reported in migraine attacks.

- Efficacy of NSAIDs as acute/preventive therapies for migraine supports a role for PGs

- Receptors for PGs, particularly PGE2 and PGEI2, are targets for migraine therapy.

# Migraine- associated sensory sensitivity

- Migraine pain continues to be worsened by light in patients in whom rod and cone damage cause blindness, indicating that there are alternative pathways for mediating light sensitivity in migraine, possibly a direct pathway from the retina to a region of the posterior thalamus that also responds to stimulation of the dura.

- The occipital cortex is shown to be hyperexcitable in association with migraine photophobia independent of headache.

- The thalamus may also play a key role in sensory sensitivity during migraine.

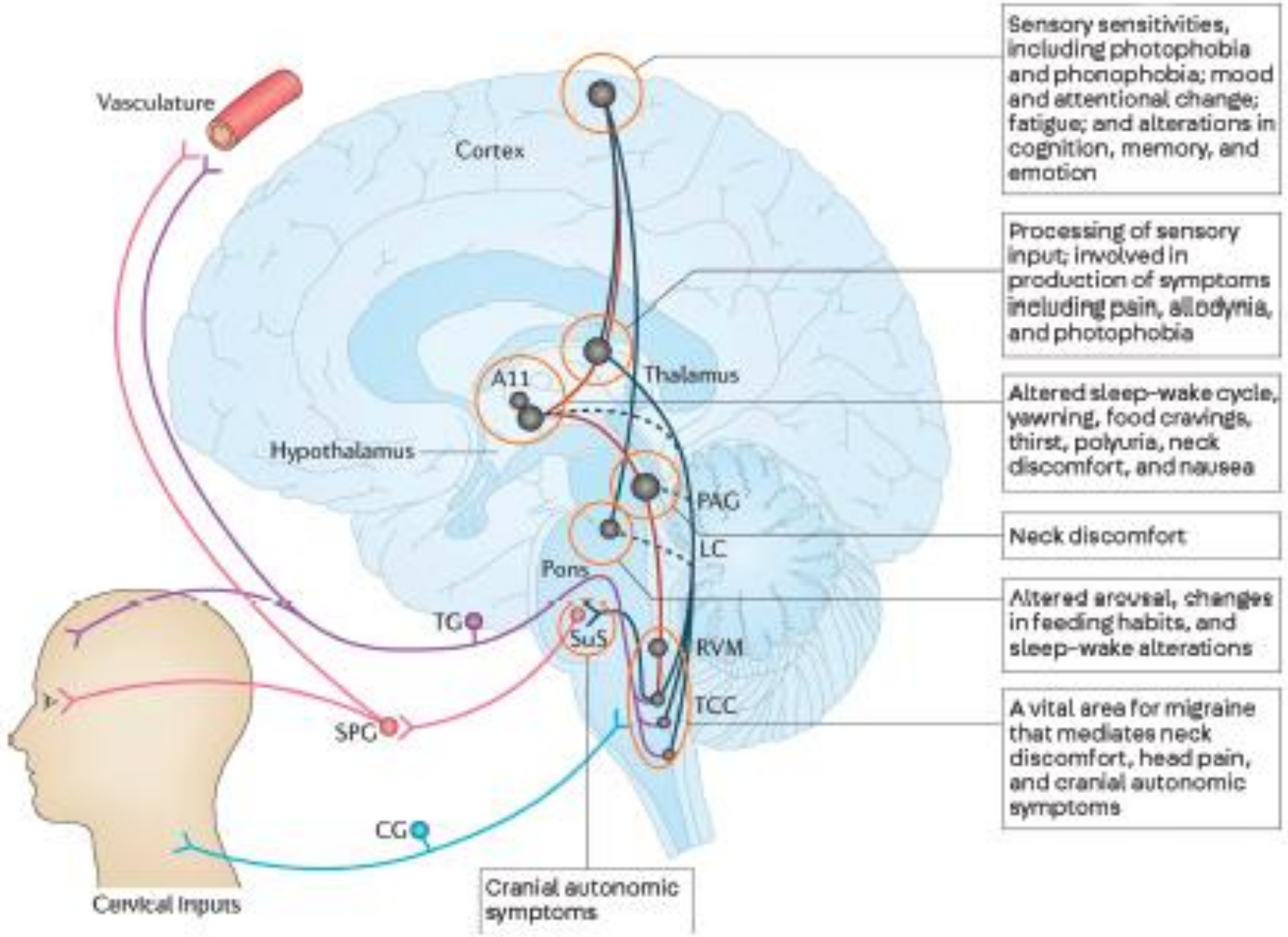
- Mechanical and thermal allodynia associated with migraine are associated with increased thalamic responses to sensory stimulation based on fMRI blood oxygen level- dependent imaging.

# Chronic changes with chronic headache

- Migraine is associated with long- lasting changes in regions of the brain including a decrease in gray matter volume in the anterior cingulate and insular cortex, and thalamus, orbitofrontal, prefrontal, and somatosensory cortex. Also Increase in gray matter volume in the periaqueductal gray and in the dorsal pons in the brainstem.

- The extent of gray matter decrease was correlated with the duration of the disorder.

- Interictal levels of CGRP in peripheral blood have been reported to be significantly higher in patients with chronic migraine particularly who had a history of migraine with aura. These findings provide support for preventive therapies targeting CGRP and its receptor.




Trigeminal afferents converge with cervical afferents from the upper cervical dorsal root ganglion (CG) in the trigeminocervical complex (TCC) in the brainstem and upper cervical spine.

Second-order neurons from the TCC project to the thalamus, from which thalamocortical neurons relay sensory information to multiple cortical areas.

Several structures, such as the rostroventral medulla (RVM), locus coeruleus (LC), periaqueductal gray (PAG), and hypothalamic nuclei, have been implicated in trigeminovascular sensory modulation.

The parasympathetic pathway mediates cranial autonomic symptoms through the superior salivatory nucleus (SuS) and the sphenopalatine ganglion (SPG).


MAYO
CLINIC

*Thanks*