MIGRAINE PATHOPHYSIOLOGY – WHAT'S NEW?

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Migraine Genetics

-Genome wide associations studies continue to identify more gene polymorphisms that are associated with either increased or decreased propensity to migraine.

- At present count there are 38 susceptibility loci for migraine based on meta-analysis(1) .
- These loci all have small effect sizes, meaning that no single gene is clearly implicated in migraine in the general population (2).
- Studies are underway to determine if there is a shared genetic basis for migraine and other disorders like vascular disease or stroke based upon these population studies

Migraine pharmacology

-Serotonin

- A clinical trial of the medication lasmiditan reported efficacy of this selective 5HT1F agonist as an acute migraine therapy .
- Since 5HT1F receptors are not believed to be expressed in significant amounts on blood vessels, and since lasmiditan does not constrict blood vessels in animal models, the efficacy of lasmiditan adds to now substantial evidence that vasoconstriction is not a required mechanism for acute migraine therapies (3)
- The CNS side effects of lasmitidan provide indirect evidence that it may be working in the brain

-CGRP (Calcitonin Gene Related Peptide)

- Multiple Phase 2 and Phase 3 trials of small molecules or antibodies targeting CGRP or its receptor studies provide further support for the concept that CGRP plays a primary role in the pathogenesis of migraine, at least in some individuals (4) (5-9)
- The site of action of therapies targeting CGRP remains uncertain, although it is clear that CGRP may be involved in migraine related mechanisms both in the central and peripheral nervous system
- The prolonged duration of therapeutic effect reported in some of these trials raises the possibility that targeting CGRP could have "disease-modifying" effects

Migraine physiology

- Further studies have quantified changes in sensory sensitivity in the hours preceding headache, and neurophysiological studies have also demonstrated changes in sensory circuits leading up to headache, providing additional evidence of important changes in brain activity in the premonitory phase of migraine (10, 11)
- An interesting study in which a single patient was studied with fMRI on a daily basis for 30 days confirmed previous studies indicating a role for the hypothalamus as a potentially important early mediator of a migraine attack. (12) (13)
- Other studies indicate changes in the activity of thalamo-cortical circuits in the premonitory phase, indicating that the thalamus may also play a critical role in the generation of migraine. (14) (15)

Migraine and the blood brain barrier

- For decades there has been speculation that migraine attacks could be associated with breakdown of the blood brain barrier.

-PET studies now provide strong evidence that therapeutic concentrations of migraine treatments do not show significant penetration of the blood brain barrier, and indicate that BBB remains intact during a migraine attack (16)

- It is important to keep in mind, however, that migraine-related receptors (such as CGRP receptors) are expressed in brain regions (notably the hypothalamus) that are outside of the blood brain barrier. (17)

Migraine and vascular disease

- A study reported increased risk of peri-operative stroke in patients with migraine with aura . (18)
- The basis for the relationship between migraine and stroke remains unclear
- Meta-analysis of multiple studies indicates a specific relationship between migraine with aura and patent foramen ovale, raising the possibility that this relationship could be responsible for the risk of stroke in patients with migraine with aura . (19)

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