Migraine Pathophysiology: What’s New?

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DISCLOSURES

- Grant Support
  - Takeda
- Consultant
  - Amgen, Alder, Biohaven, Eli Lilly, eNeura, Trevena
- Clinic Trial Steering Committee
  - St. Jude
Advances in Migraine Genetics

NO ASSOCIATION BETWEEN PARanasal sinUS OpACIFICATION AND MIGRAINE OR TENSION TYPE HEADACHE
10.1 Headache attributed to hypoxia and/or hypercapnia

10.1.1 High-altitude headache
10.1.2 Headache attributed to aeroplane travel
10.1.3 Diving headache
10.1.4 Sleep apnoea headache
TRP channels as therapeutic targets

- Activation of TRPA1 channel by umbellulone (from "headache tree") triggers cluster-like headache
- Polymorphisms of TRPM8 channels consistently associated with migraine in GWAS studies
- TRP channels widely expressed in trigeminal nociceptive pathways

Migraine and Right-to-left Shunt

- Migraine with aura associated with patent foramen ovale
- Migraine with aura associated with pulmonary right to left shunt in hereditary hemorrhagic telangiectasia
- Multiple negative studies of PFO closure for migraine with and without aura

HOWEVER....
Could PFO be responsible for increased stroke risk in migraine patients?

- In recent PREMIUM study, exploratory secondary analysis showed that PFO closure had significant benefit for patients with aura with the majority of their attacks.
- Recent studies showed that PFO closure beneficial for stroke prevention.
- Review of UCLA Stroke database indicates that PFO present in the majority of those with cryptogenic stroke, and:

CGRP and CSD

The CGRP Receptor Antagonist Olcegepant Inhibits CSD
S. Eftekhar
What Do Clinical Trials of CGRP-related Therapies Tell Us About Pathophysiology?

Exciting Results with Monoclonal Antibodies against CGRP or its Receptor

- Rapid onset of therapeutic effect
- Sustained duration of therapeutic effect – (3-12 months)
- “Super responders” – significant subset of patients with 75% reduction in migraine days and small subset with 100% reduction in migraine days

Conclusions from CGRP Clinical Trial Data

- Specificity of antibodies to targets definitively proves primary role for CGRP and CGRP receptor in migraine
- Efficacy of antibodies, which presumably do not cross blood brain barrier, indicates mechanism of action that is either peripheral, or in brain regions outside of BBB
GENES >

Migraine associated gene polymorphisms

ENVIRONMENT
Barometric pressure
Stress

HORMONES
Menstrual cycle
Pregnancy

DRUGS
Exacerbating medications

METABOLISM
Diet
Neuroendocrine function

Hypothalamic activation
Alteration in thalamocortical circuits
Altered brain connectivity

Hormonal and metabolic state
Migraine genes

Variable Attack Symptoms and Severity
Premonitory Aura Headache Postdrome

Brainstem Activation
CSD
CGRP
PACAP
Release

Cervical nerve anatomy

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