Faculty of Health and Medical Sciences

Targeting ion channels

The 3rd Nordic Migraine Symposium 26-27 November 2021

Messoud Ashina, MD, PhD, DMSc, FEAN
Professor of Neurology

Rigshospitalet Glostrup

Disclosures

Personal fees from AbbVie/Allergan, Amgen, Eli Lilly, Lundbeck, Novartis and Teva. MA participated in clinical trials as the principal investigator for AbbVie/Allergan, Amgen, Eli Lilly, Lundbeck, Novartis and Teva.

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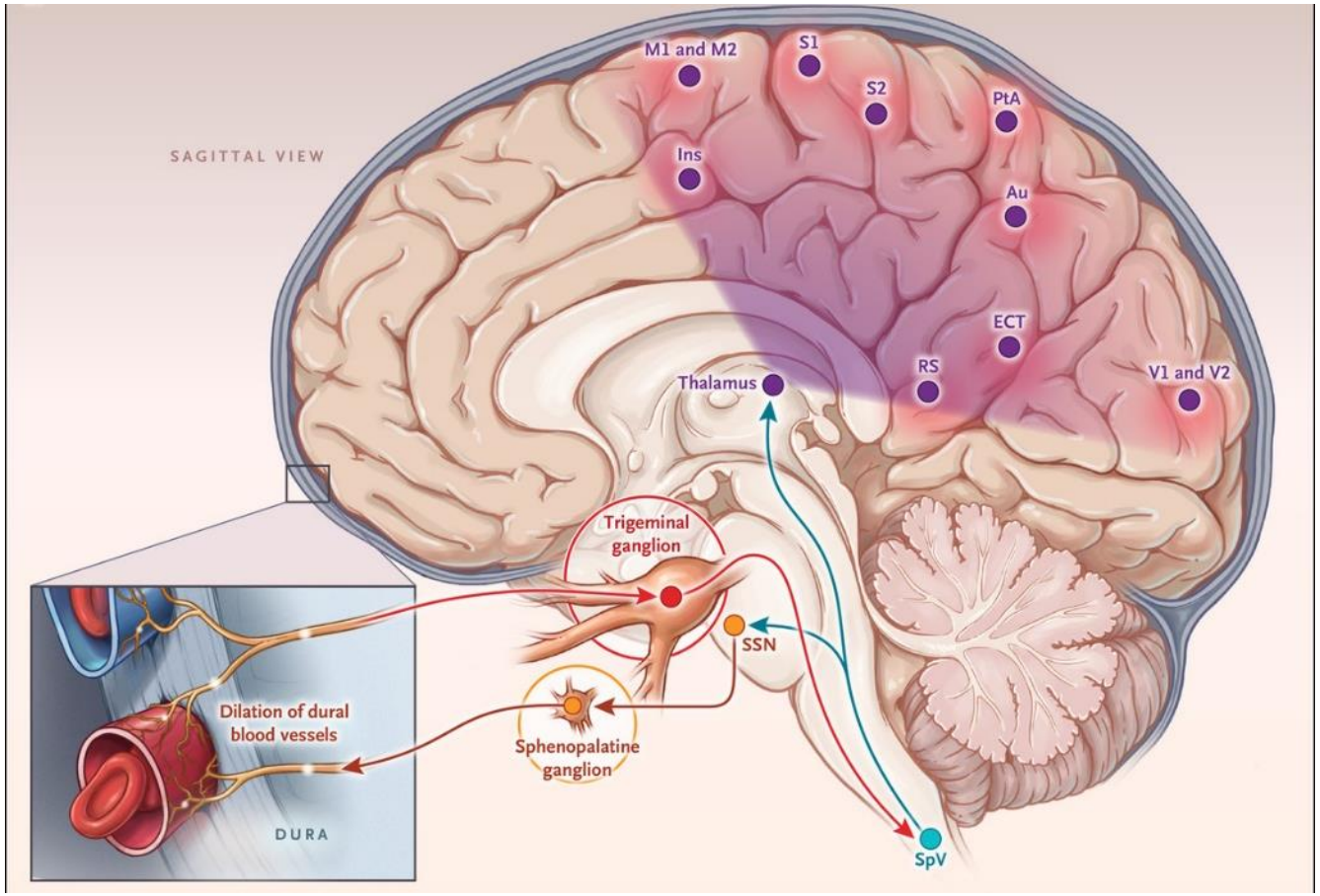
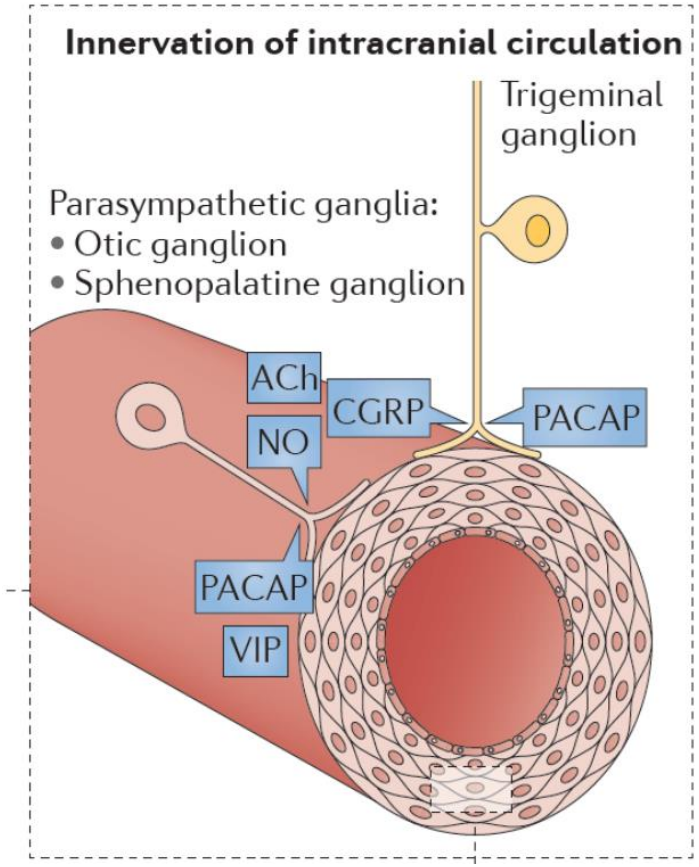
MA has no ownership interest and does not own stocks of any pharmaceutical company.

MA serves as associate editor of Cephalalgia, associate editor of the Journal of Headache and Pain, and associate editor of Brain.

The **trigeminovascular** system

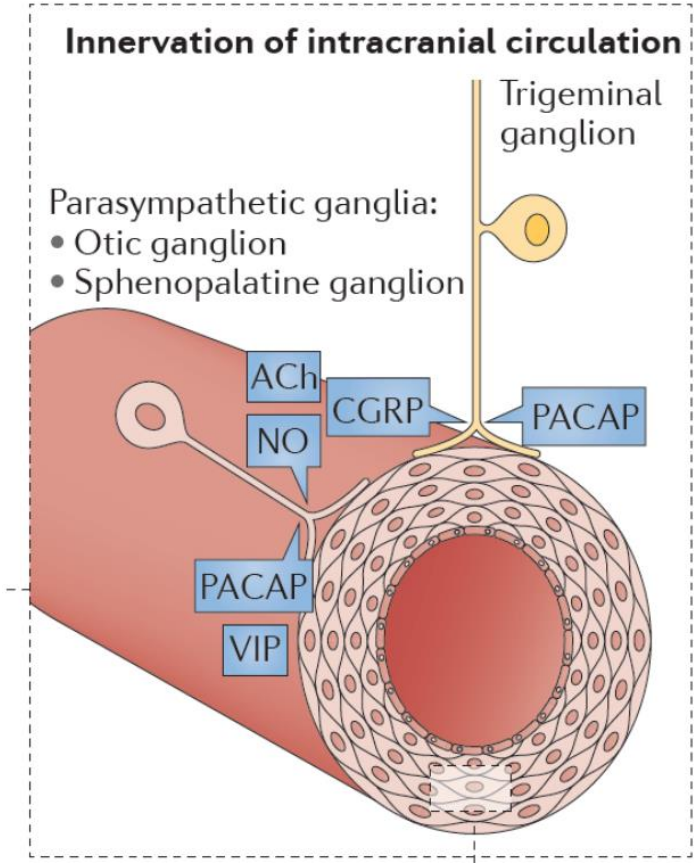




ACh, acetylcholine; CGRP, calcitonin gene-related peptide; NO, nitric oxide;
PACAP, pituitary adenylate cyclase-activating polypeptide; VIP, vasoactive intestinal peptide.

Ashina M, et al. *Nat Rev Neurol* 2017;
Ashina M, et al. *Lancet Neurol* 2019;
Ashina M. *N Engl J Med* 2020.

Triggering migraine



Ashina M, et al. *Nat Rev Neurol* 2017;13:713–24;

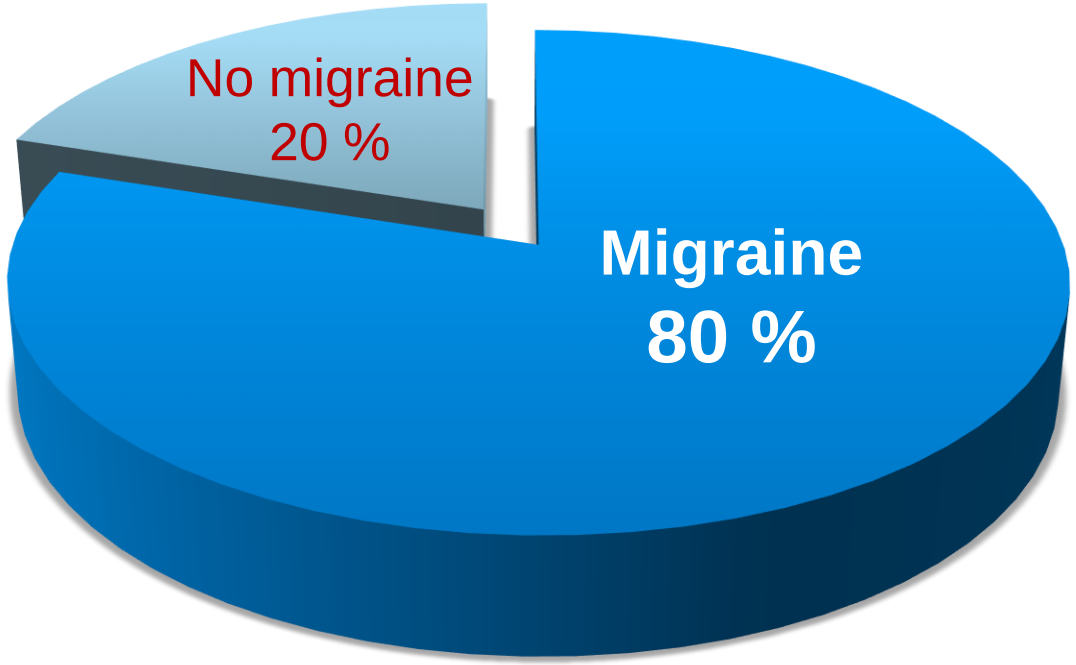
CGRP, PACAP38, PGE2, NO, VIP

Modified from Vollesen and Ashina. *Headache* 2017

Exploring signaling pathways in migraine

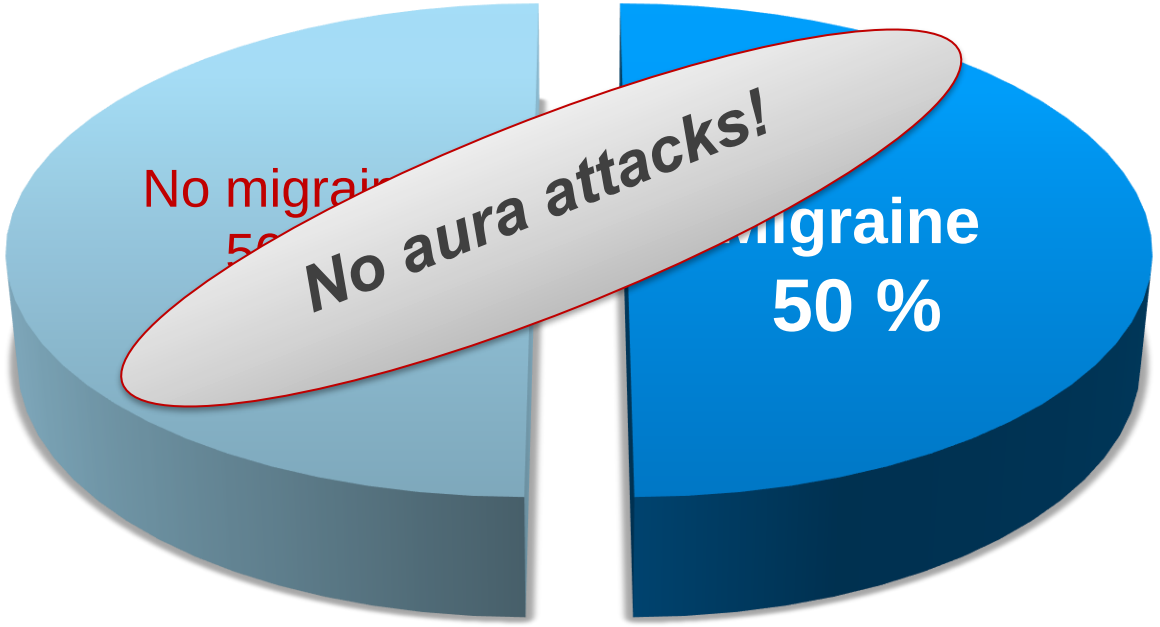
Lessons from triggering attacks with glyceryl trinitrate

Patients with migraine *without* aura



Thomsen et al. *Eur J Neurology* 1994

Patients with migraine *with* aura

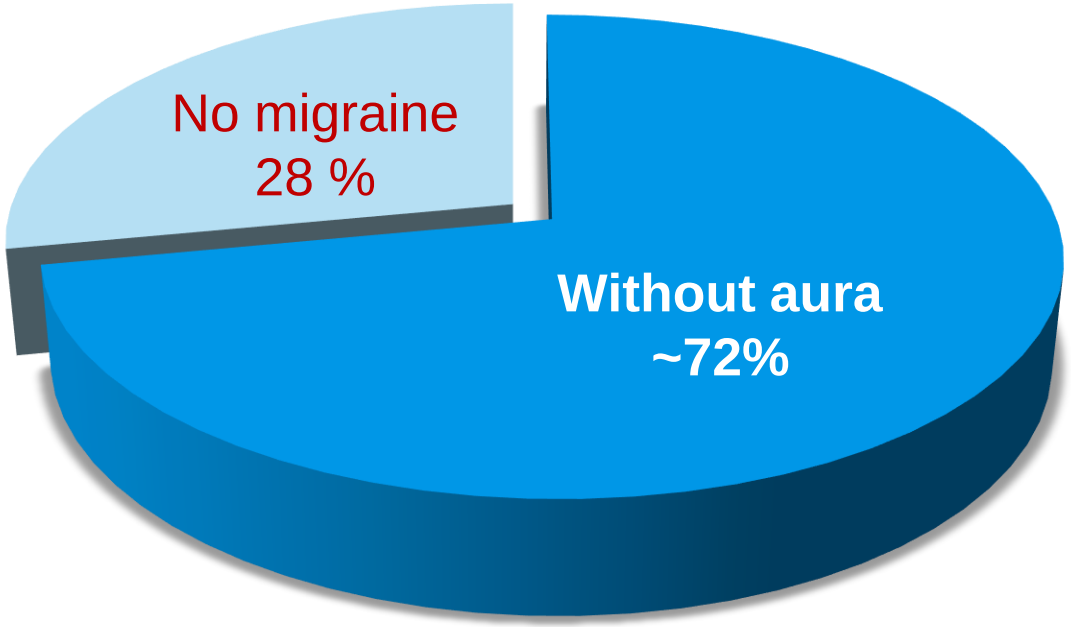


Christiansen et al. *Cephalalgia* 1999

CGRP and PACAP induces migraine attacks

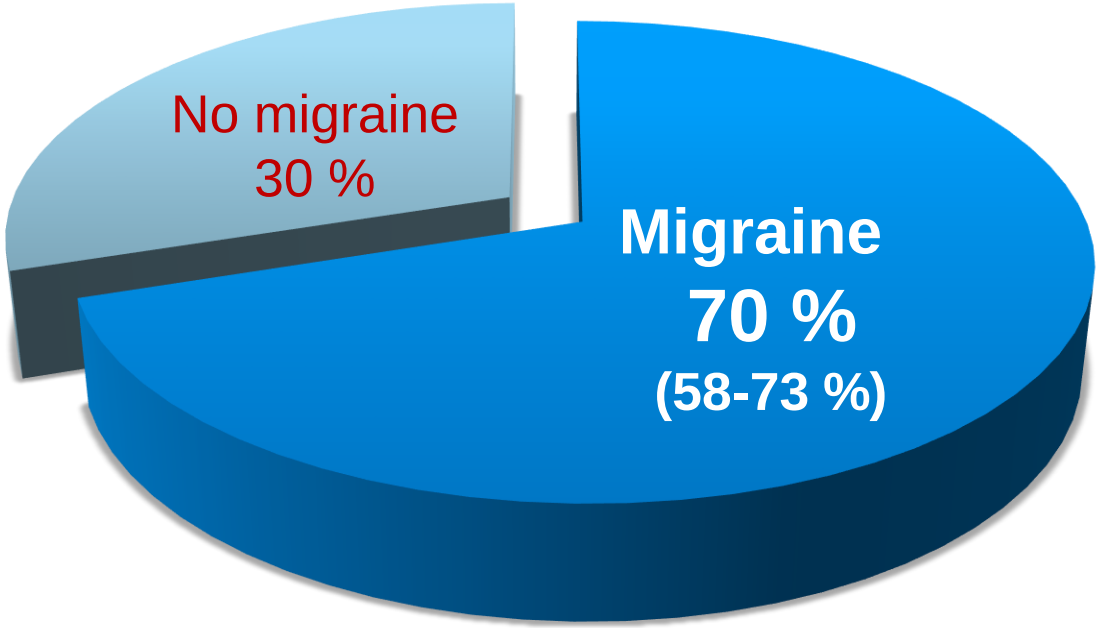
CGRP

Patients with migraine with and without aura[2–4]



PACAP

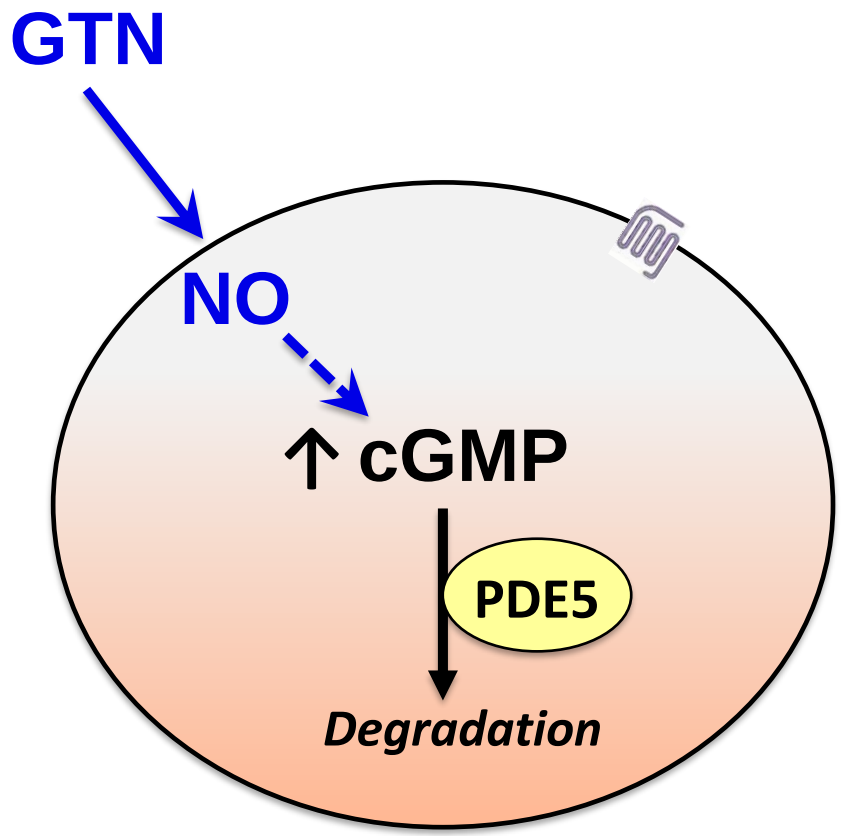
Patients with migraine *without* aura



Ashina M, et al. Nat Rev Neurol 2017; Schytz et al. *Brain* 2009; Hansen JM, et al. *Cephalalgia* 2010; Amin et al. *Brain* 2014; Guo et al. *Cephalalgia* 2014; Guo S, et al. *Cephalalgia* 2017; Asghar MS, et al. *Ann Neurol* 2011.

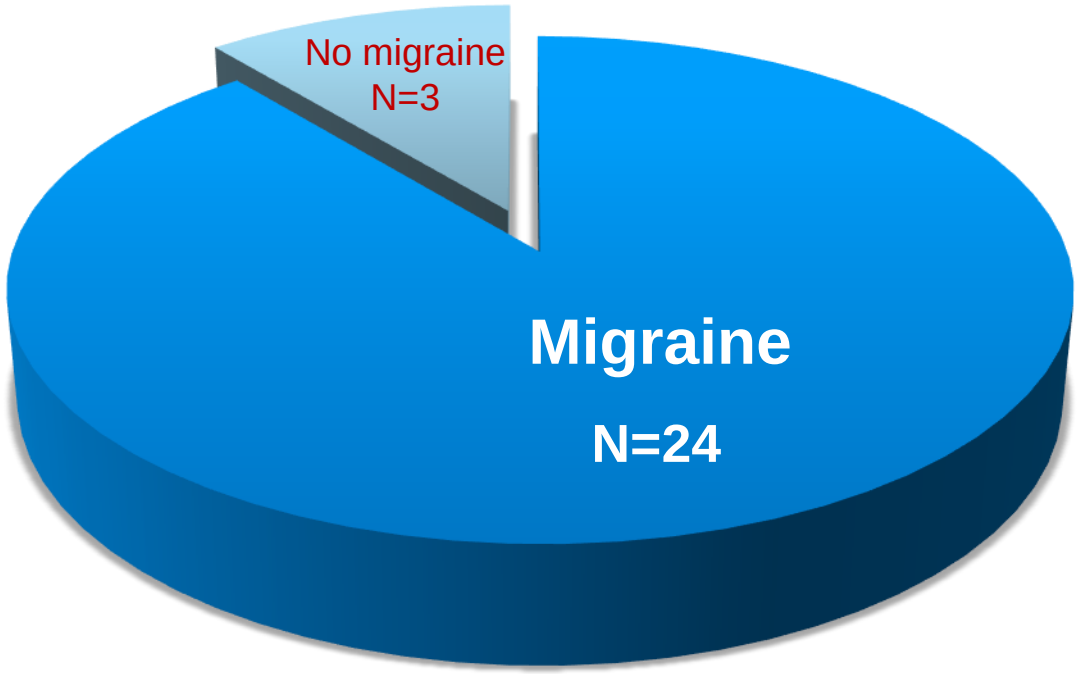
Targeting downstream signaling pathways

Signalling pathways that initiate migraine attacks



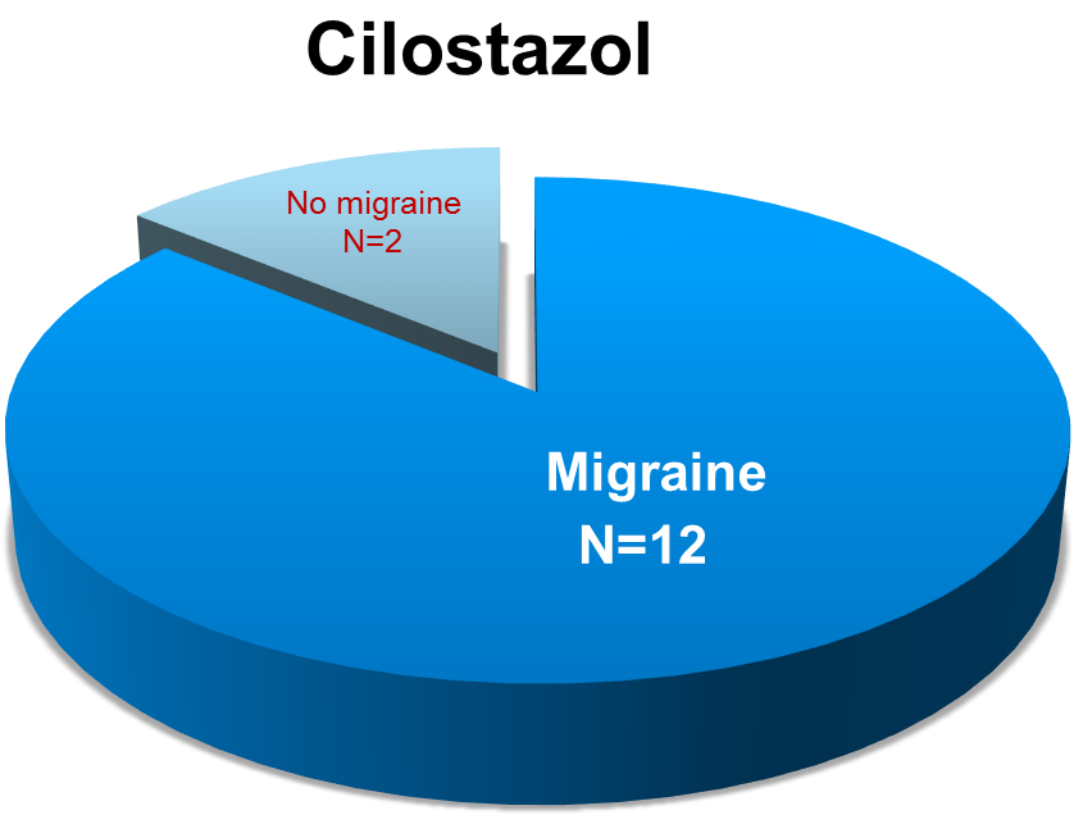
Sildenafil

Sildenafil

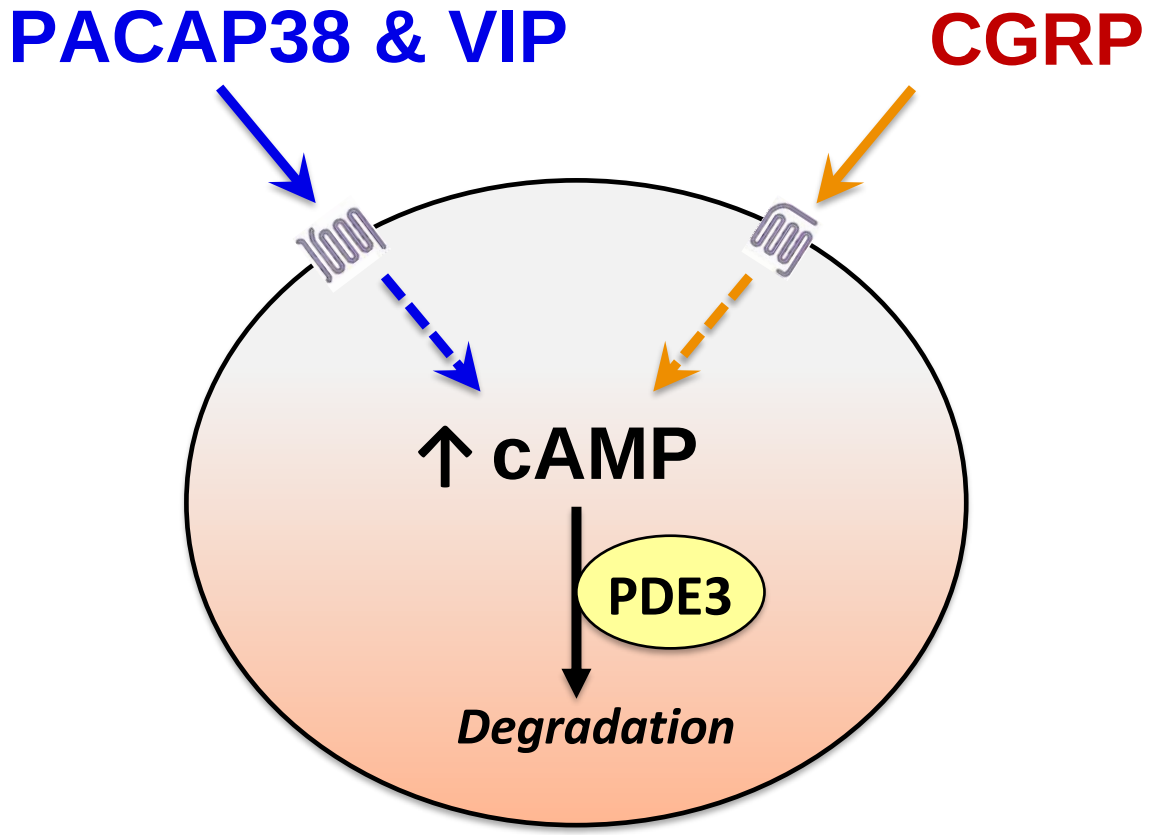


Younis et al. *Cephalalgia* 2019

Signalling pathways that initiate migraine attacks

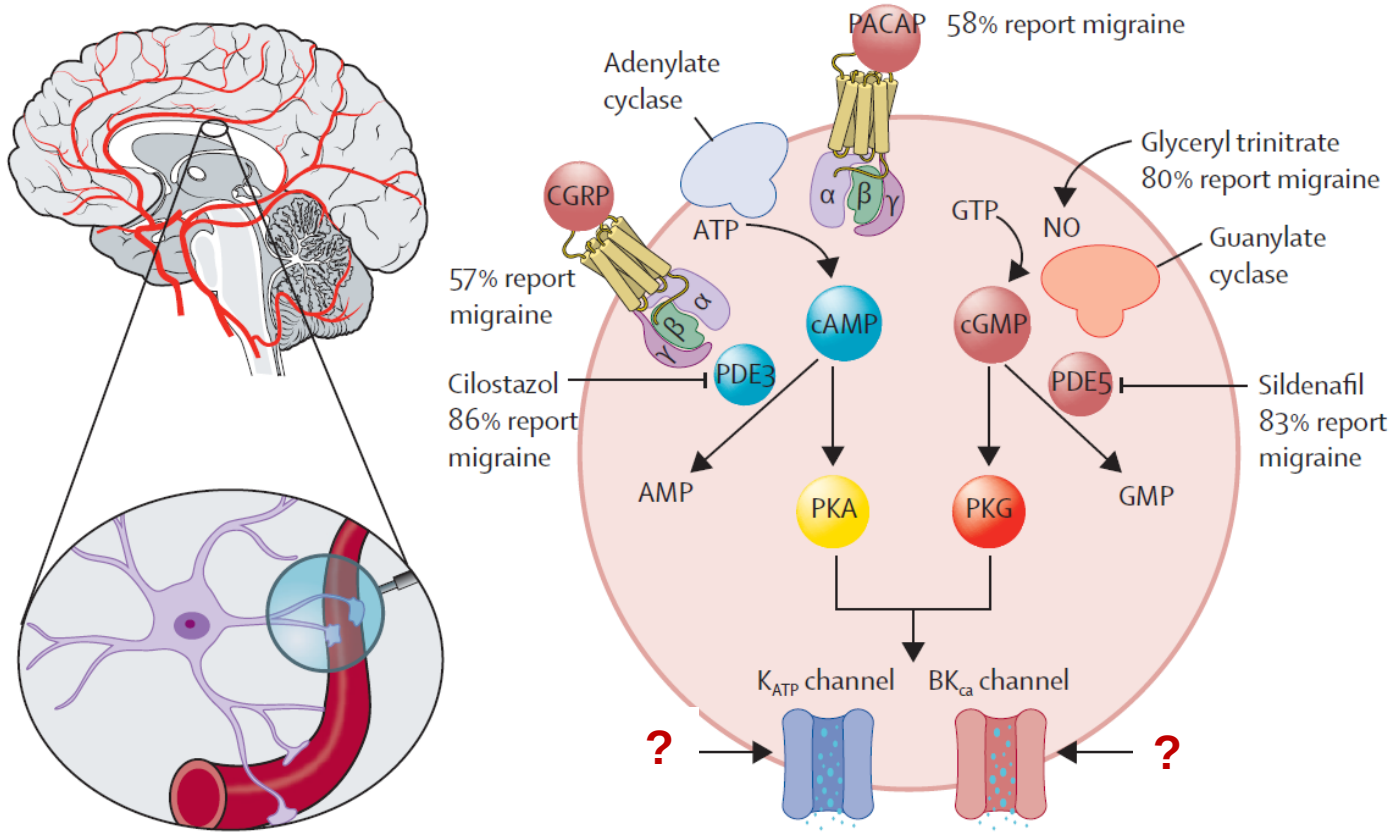


Guo et al. *Brain* 2014



Cilostazol

Signaling pathways responsible for the genesis of a migraine attack



Cell is a vascular smooth muscle cell

K_{ATP}: ATP-sensitive potassium channel
BK_{Ca}: large conductance calcium-activated potassium channels

Modified from Ashina M, et al. *Lancet.* 2021;397(10283):1496–1504.

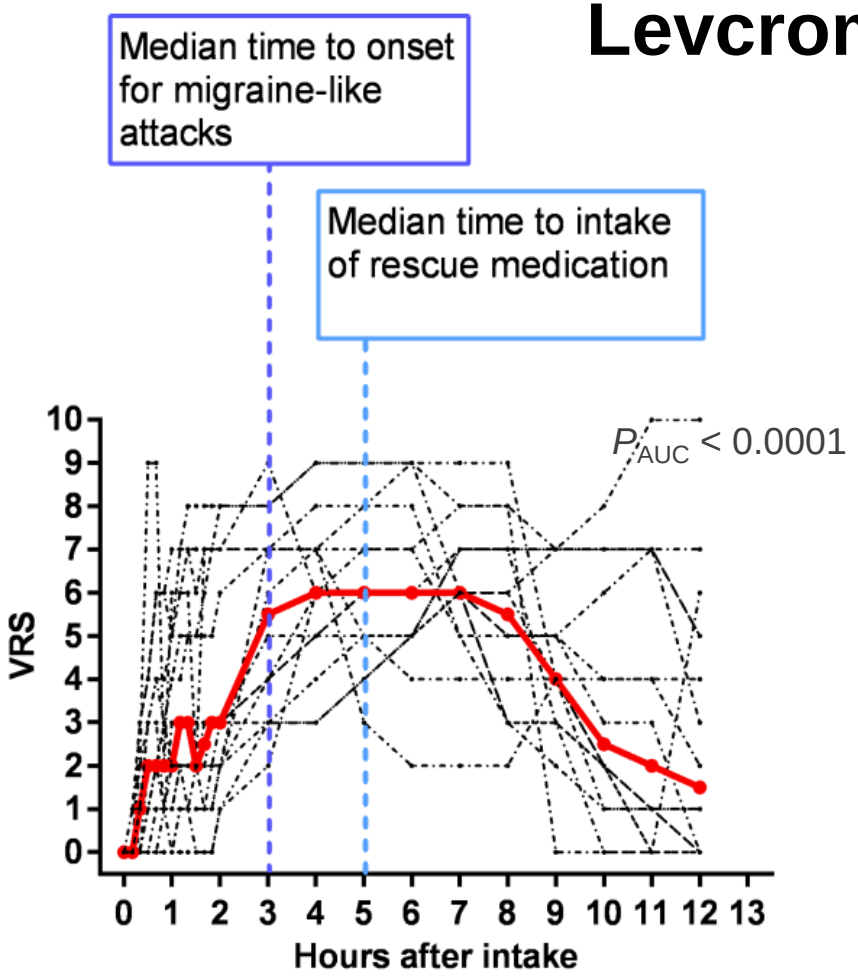
Targeting K_{ATP} and BK_{Ca} Channels in Migraine: Rationale

- K_{ATP} and BK_{Ca} channels are expressed in migraine-related structures such as the cranial arteries, trigeminal ganglion and trigeminal spinal nucleus
- K_{ATP} and BK_{Ca} channels are also activated by several key molecules in migraine pathogenesis, such as nitric oxide, CGRP, PACAP38, cilostazol, sildenafil and nitric oxide
- Synthetic K_{ATP} and BK_{Ca} channel openers provoke headache

K_{ATP}: ATP-sensitive potassium channel
BK_{Ca}: large conductance calcium-activated potassium channels

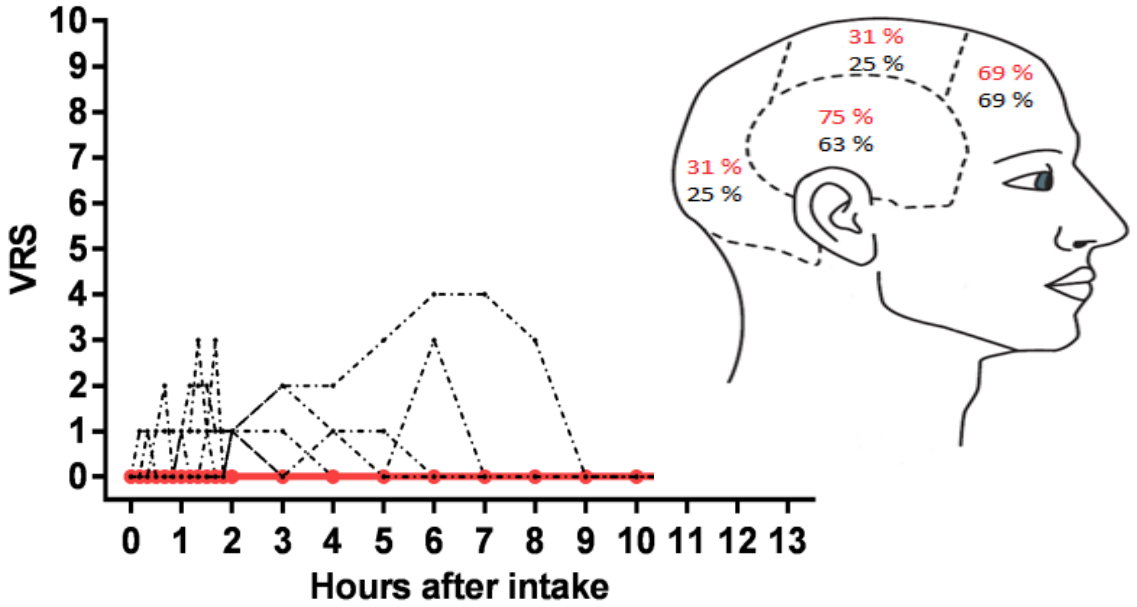
Al-Karagholi et al. *J Headache Pain* 2017
Al-Karagholi MA al. *CNS drugs* 2020

Levcromakalim induced migraine *in all patients*



Median headache score (Levcromakalim)

Migraine attacks induced by levcromakalim.
Spontaneous migraine attacks.

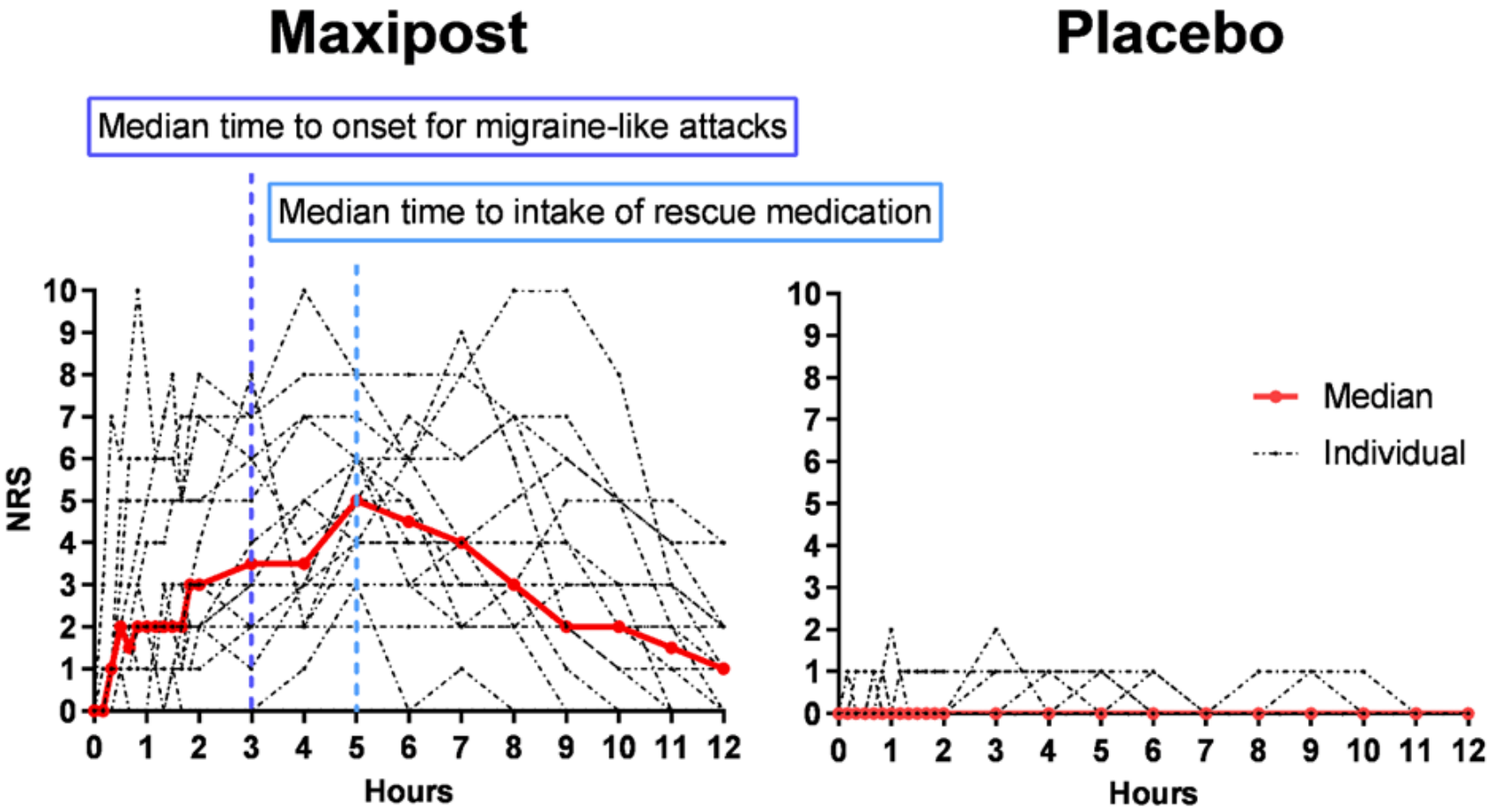


Median headache score (placebo)

Al Karagholi et al. *Brain* 2019

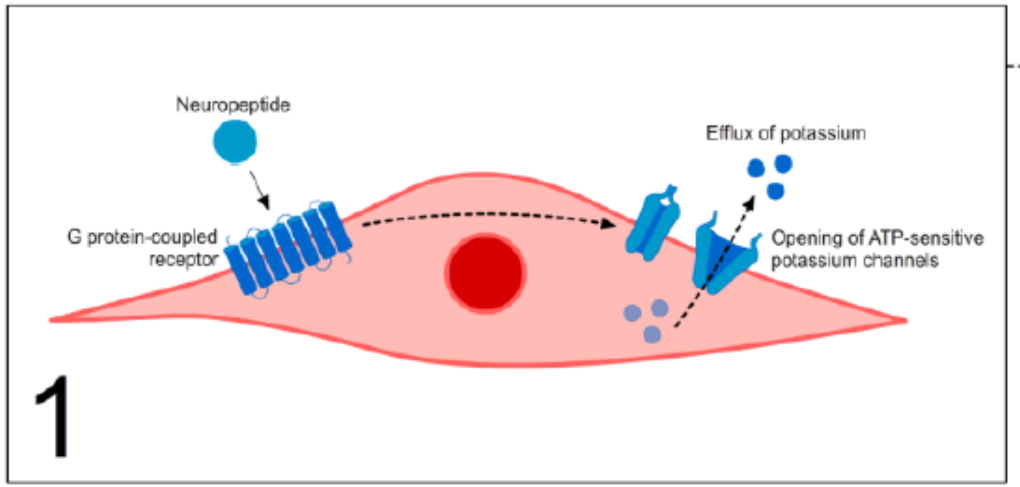
Targeting BK_{Ca} Channel opener induced Migraine Attacks

95 % of patients

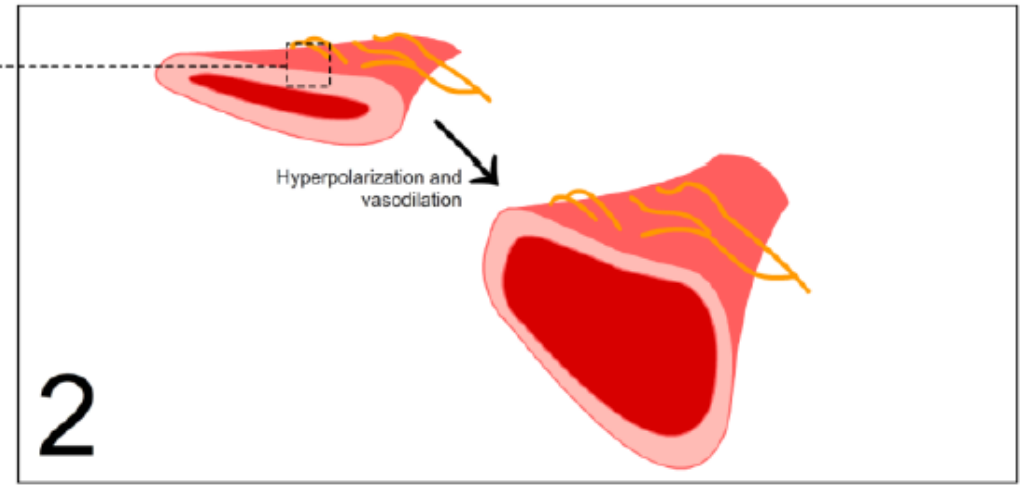


Al Karagholi et al. Pain, 2021 Oct 1;162(10):2512-2520

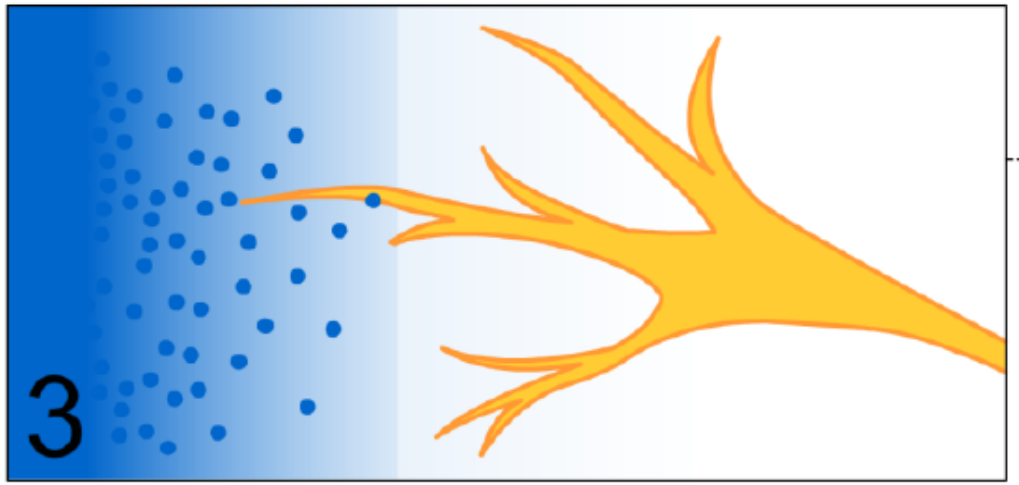
Figure S2: A Proposed Trigeminovascular Ion Channel Hypothesis of Migraine Pathogenesis.



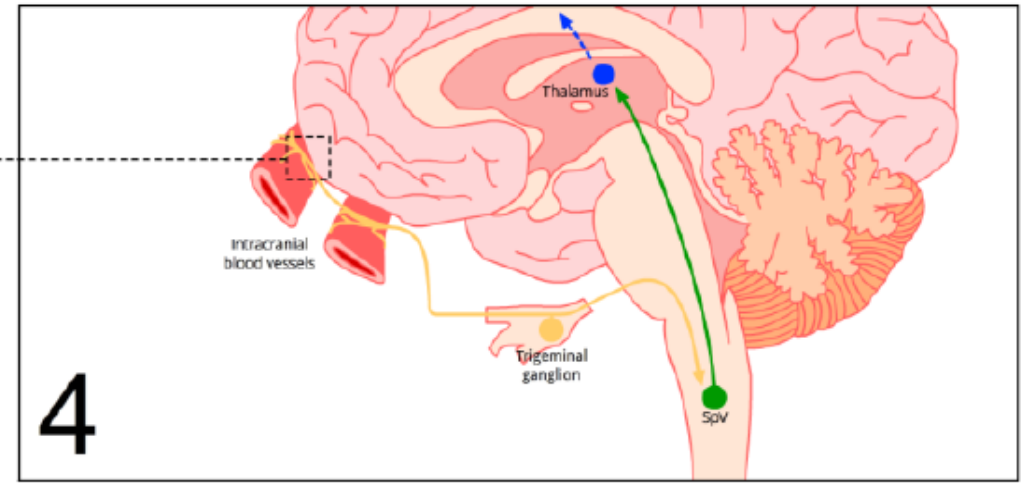
Opening of ATP-sensitive potassium channels on vascular smooth muscle cells intracranial arteries



Efflux of potassium causes hyperpolarization and vasodilation of these arteries



Increase in extracellular potassium sensitize and discharge perivascular trigeminal primary afferents



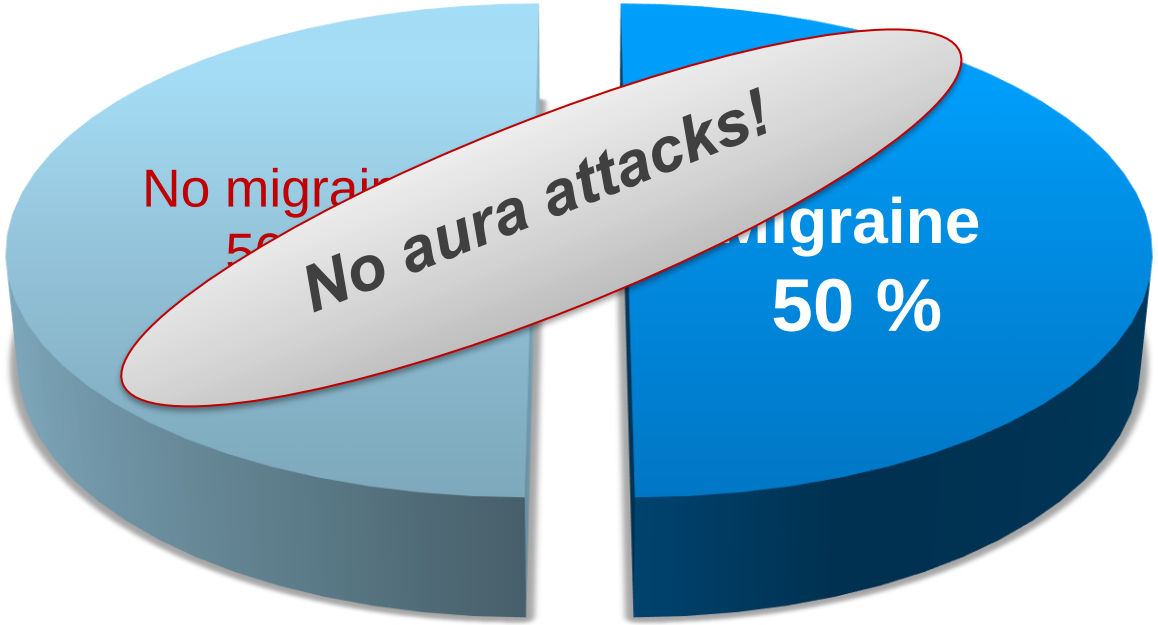
Nociceptive impulses are transmitted to cortical and subcortical regions via trigeminal pain pathways

Supplement to: Ashina M. Migraine. *N Engl J Med* 2020;383:1866-76. DOI: 10.1056/NEJMra1915327

Molecular signal pathways leading to aura

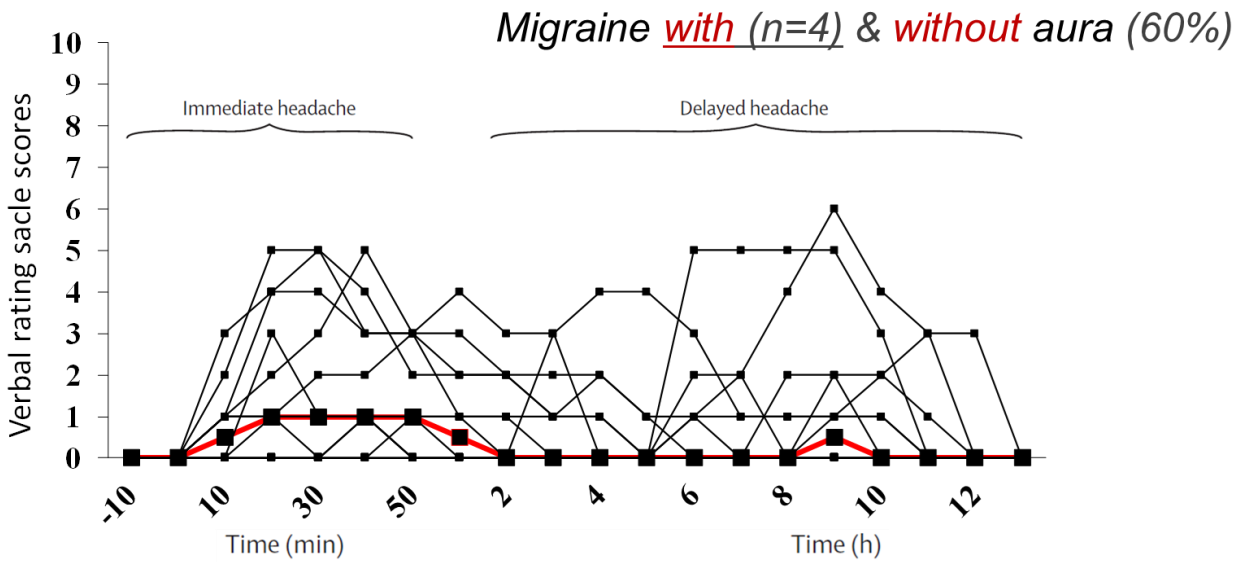
Triggering migraine with aura

Patients with migraine *with* aura
GTN infusion



Christiansen et al. *Cephalalgia* 1999

Patients with migraine *with* aura
CGRP infusion



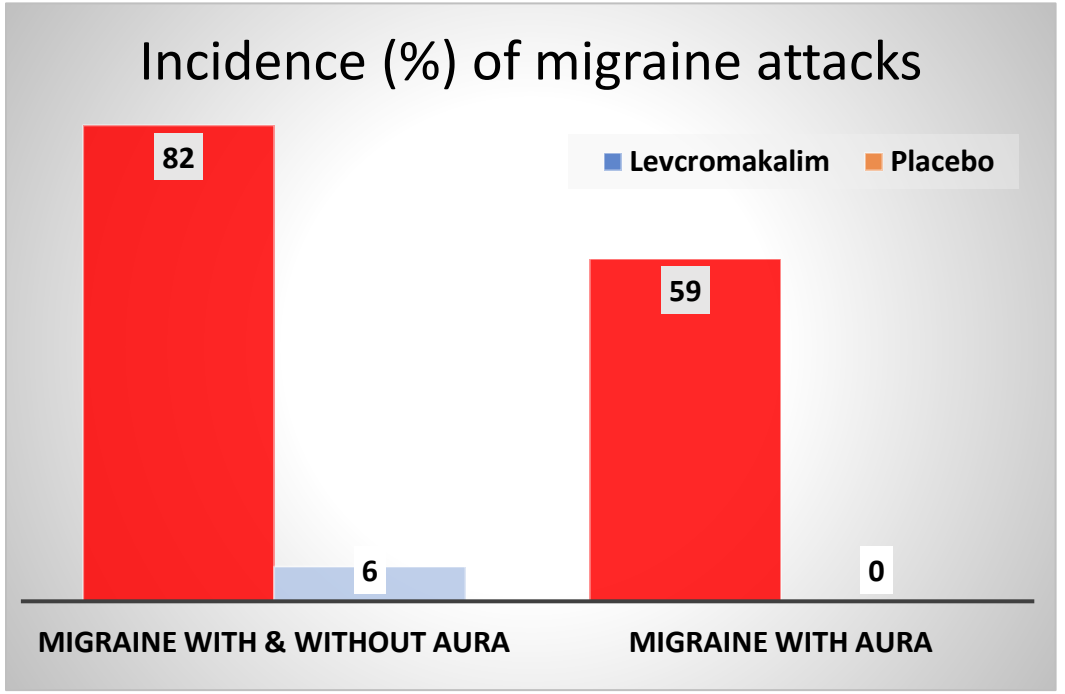
Hansen et al. *Cephalalgia 2010*

K_{ATP} channels and migraine aura

Hypothesis: levcromakalim triggers migraine attacks with aura.

Al-Karagholi et al. *Brain* 2021

The ATP-sensitive potassium channel opener levcromakalim triggers migraine with aura



Al-Karagholi MA et al. *Brain* 2021

The ATP-sensitive potassium channel opener levcromakalim triggers migraine with aura

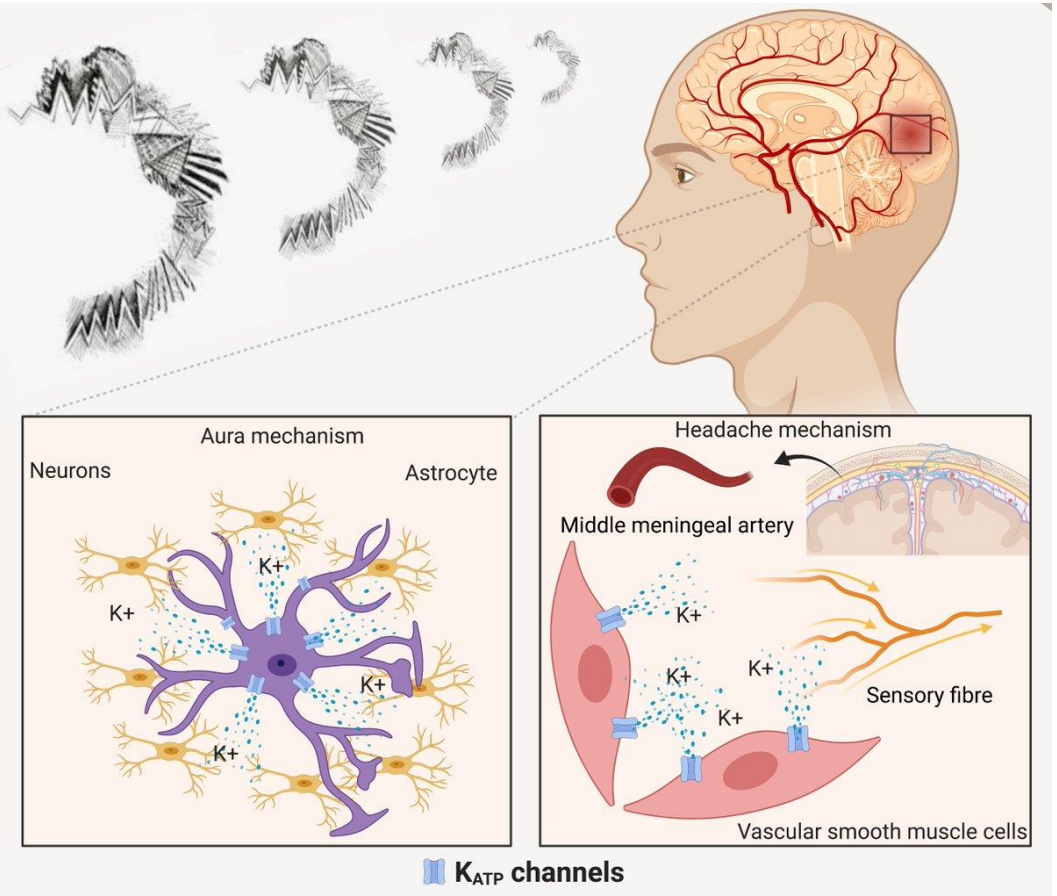
Possible mechanisms

- Activation of K_{ATP} channel expressed on glial cells causes K^+ efflux and an increase in $[K^+]_o$.

→ migraine aura

- Activation of K_{ATP} channel expressed on vascular smooth muscle cells causes K^+ efflux and a sensitization of meningeal afferents.

→ migraine headache



Al-Karagholi et al. *Brain* 2021

Conclusions

- Opening of K_{ATP} channels causes migraine attacks with and without aura
- Opening of BK_{Ca} channels causes migraine attack without aura
- Opening of these channels is the strongest provocation of migraine ever studied
- We suggest blocking of these channels as a new therapeutic target downstream from signaling molecules

Ashina M. *N Engl J Med* 2020;383:1866-1876.
Ashina M et al. *Lancet* 2021;397(10283):1496-1504.

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Participants

- Migraine patients and healthy volunteers

Colleagues