Research round-up

Highlights from headache studies. By Anthony King

ILLUSTRATION BY TAJ FRANCIS

Migraine trigger target

Researchers at the Danish Headache Center in Copenhagen have identified a molecule that opens potassium channels as the most powerful inducer of migraines ever tested in people — suggesting that the channels it targets could be of therapeutic interest.

Giving pharmacological substances to people with migraine to see whether they induce an attack can provide considerable insight into the disorder. The strategy helped to uncover the role of the receptor for calcitonin gene-related peptide (CGRP), for example, which has led to numerous therapies.

In the most recent work, Messoud Ashina and his colleagues probed the role of ATP-sensitive potassium channels (K_{ATP}) in migraine attacks. These channels stud cells in cranial arteries and the trigeminal nerve of the face, which is thought to be centrally involved in headache. The researchers opened the channel using levcromakalim, a drug that is used to reduce people's blood pressure and is also known to cause headaches.

Sixteen people received either levcromakalim or a placebo on two days. All of those given an infusion of levcromakalim had a migraine attack, compared with just one person who received a placebo. The results suggest that K_{ATP} channels have a role in migraine attacks, perhaps late in the migraine pathway, and should be investigated as a potential target for future drugs.

The next step for Ashina and colleagues is to find compounds that selectively target the subtype of K_{ATP} channel found in brain arteries and the trigeminal nerves.

Brain **142**, 2644–2654 (2019)

Dynamite model verified

Nitroglycerine, a component of dynamite, has long been used by researchers to generate migraine-like headaches. Some scientists have questioned whether it mimics a true migraine attack in humans, but this model has now received a boost.

A 2019 study by Simon Akerman at the University of Maryland, Baltimore, and his colleagues shows that nitroglycerine triggers allodynia, a symptom of migraine in which non-painful stimuli, such as touching the face or combing hair, provoke pain. This adds to evidence that nitroglycerine causes an attack that closely mirrors what happens naturally.

The researchers administered nitroglycerine to 53 people with a history of migraine. They found that people who experience cranial allodynia during spontaneous migraine attacks were significantly more likely to have it during a nitroglycerine-triggered attack. And the participants responded to treatment with aspirin or sumatriptan, as with spontaneous migraine.

The team also administered nitroglycerine to rats, a common animal model, and looked at neuronal activity in regions of the brain that are active during migraine. They found signatures of trigeminal-nerve firing and cranial allodynia. Additionally, as in people, an anti-migraine drug relieved sensitivity to touch. This provides reassuring evidence for researchers who use nitroglycerine in rodent models of migraine for drug discovery.

Brain **142**, 103–119 (2019)

A first-in-class approval

A therapy for acute migraine with a new mechanism of action has received approval in the United States. It is expected to particularly benefit people with cardiovascular conditions that prevent them from taking some existing medications.

The most widely used specific migraine therapies are triptans, which block the receptor for the neurotransmitter serotonin 1B. However, this causes blood vessels to

constrict and increases blood pressure. As a result, people with cardiovascular conditions or those at an increased risk of heart disease or stroke are advised to avoid triptans — which is a problem, because cardiovascular comorbidities are common in migraine.

In October 2019, the US Food and Drug Administration approved lasmiditan tablets for the treatment of acute migraine. Like triptans, lasmiditan acts on the trigeminovascular system — the network of nerves linked to blood vessels in the head — but instead has a high affinity for the serotonin 1F receptor, the blocking of which does not cause vasoconstriction.

In a phase III clinical trial that supported the approval, Richard Lipton at Albert Einstein College of Medicine in New York City and his colleagues randomized 2,231 adults with migraine to receive either 100 milligrams or 200 mg of lasmiditan or a placebo when they had a migraine attack. Those who received lasmiditan were more likely to be free of both pain and their most-bothersome other symptom, such as nausea, two hours after taking the drug.

Adverse cardiovascular events were low, with less than 1% reporting palpitations. Most side effects were related to the nervous system: about 14% of those who received lasmiditan reported dizziness.

Neurology **91**, e2222–e2232 (2018)

Acupuncture evidence gathered

A randomized controlled trial of acupuncture in people who experience migraine without aura suggests that the therapy could be effective in preventing migraine attacks.

Wei Wang at Huazhong University of Science and Technology in Wuhan, China, and his colleagues tested manual acupuncture — the insertion of needles into points on the body — in 150 people who experience episodic migraine without aura. The participants were divided into three groups that, over 8 weeks, received 20 sessions of manual acupuncture alongside their usual care; 20 sessions of a sham procedure and their usual care; or their usual care alone.

In each session, needles were applied to at least ten points on the person's body. The needles used in the sham treatment had a blunt tip, to give a pricking sensation without penetrating the skin. In an effort to ensure that people remained blind to whether they were receiving the real treatment, the researchers recruited only participants who said they had no prior experience of acupuncture. At the end of the study, the researchers reported no significant difference in the proportion of people who perceived skin penetration between the two groups.

Manual acupuncture resulted in a significantly greater reduction in migraine days at weeks 13–20 than did either the sham treatment or usual care alone. There was also a greater reduction in migraine attacks at weeks 17–20.

Several previous randomized clinical trials of manual acupuncture have found no improvement over a sham treatment. The authors of this study suggest that might be due to poor placebo control.

Br. Med. J. **368**, m697 (2020)

Cluster headaches zapped

A handheld device used to deliver an electrical pulse to the neck has been approved for the treatment of cluster headache in the United Kingdom. In December 2019, the National Institute for Health and Care Excellence recommended that gammaCore, a non-invasive vagus nerve stimulation (nVNS) device, should be made available through the National Health Service, on the basis of evidence from two randomized controlled trials.

Existing treatments for cluster headache include triptans, but these should not be administered to people with cardiovascular problems. nVNS can relieve attacks by generating a low-voltage signal that stimulates the vagus nerve when a person presses it against their neck.

The most recent of the two trials behind the device's approval was carried out at nine medical centres across four European countries. Peter Goadsby at King's College London and his colleagues assigned people with episodic or chronic cluster headaches to receive treatment with either the real nVNS device or an identical sham device. The sham device generated a low-frequency signal that could be felt but did not stimulate the vagus nerve.

For people with episodic cluster headaches, the nVNS device stopped 48% of attacks within 15 minutes of treatment. However, there was no significant difference between treatment with the sham and nVNS devices for people with chronic cluster headaches. This matched earlier findings.

The researchers think that stumulation of the vagus nerve might stop attacks by interfering with trigeminal nerves in the lower brain stem. However, given the broad distribution of the vagus nerve, there might be several mechanisms of action.

Cephalalgia **38**, 959–969 (2018)

One-two punch on CGRP

A drug that targets the receptor for CGRP seems to provide acute relief to people with migraine — even when they are already receiving a preventive treatment that targets the same receptor.

During a migraine attack, CGRP levels increase. Several treatments that target CGRP have been developed: small molecules called gepants that block the CGRP receptor are used as an acute treatment, and monoclonal antibodies that bind the peptide or block its receptor are used as a preventive treatment. However, because these therapies share a target, some scientists have questioned whether gepants could provide acute relief to people already receiving antibody treatment.

In January, Kathleen Mullin at the New England Institute of Neurology and Headache in Stamford, Connecticut, detailed the experiences of two people who were taking part in a long-term study of rimegepant, a small-molecule drug that was approved in the United States earlier this year. Both participants had also begun to receive monthly infusions of erenumab, a monoclonal antibody approved in 2018.

In the month after starting on erenumab, the frequency of migraine attacks declined significantly in both people, and every attack was successfully treated with rimegepant. Both stopped their regular use of other acute treatments.

It is unclear how gepants and monoclonal antibodies are able to work simultaneously to provide acute and preventive benefits. One possibility is that size matters: rimegepant is 280 times smaller than erenumab, and might be able to access receptors that the antibody cannot, such as those inside some cells.

Neurology **94**, e2121–e2125 (2020)

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