Editorial

Cephalalgia Reports

Cephalalgia Reports
Volume 3: 1–4

DOI: 10.1177/2515816320903292
journals.sagepub.com/home/rep
SAGE

Headache highlights 2019: Junior editors' choice

Kuan-Po Peng[1,2], Shih-Pin Chen[2,3,4,5], and Larus S Gudmundsson[6]

In the year 2019 in research on headache disorders, migraine remains the focus of attention as the antibodies against calcitonin gene-related peptide (CGRP) and its receptor have become available in several countries along with the publication of phase 3 clinical trials of the newer generation oral CGRP receptor antagonists.[1,2] Aside from the overshadowing CGRP research, several other interesting studies have been published. Herewith, we provide an overview of the publications that, in our opinion, contribute greatly to the understanding and treatment of headache disorders. Of note, the selection for the list is subjective and does not include all research works in the year of 2019 worthy of mention. We hope that our selection serves as a short summary and a catalyst to increase the interests of headache researchers. In the current editorial, we will discuss preclinical and clinical studies, which provide a better understanding of the disease mechanisms or a potential to future treatment targets.

Preclinical studies

Cortical spreading depression and CGRP, limited convergence

Schain et al. examined how CGRP antibodies modulate cortical spreading depression (CSD) in a rat model. The authors found that CSD-induced vascular changes of pial arteries (brief dilatation followed by prolonged constriction), prolonged dilatation of dural arteries, and plasma protein extravasation (PPE) were unaffected by the administration of fremanezumab, an anti-CGRP antibody. Additionally, CGRP infusion did not induce dilatation in pial vessels but only dural vessels, which could be effectively blocked by fremanezumab.[3] Unlike the CSD scenario whereby dilatation of dural arteries was correlated with the occurrence of PPE, the CGRP-induced dilatation of dural arteries was unassociated with PPE. Hence, although fremanezumab could block CSD-evoked activation of Aδ meningeal nociceptors and high-threshold trigeminovascular neurons,[4] the action of CGRP blockade is likely irrelevant to the CSD-evoked vascular or neurogenic inflammatory responses. Therefore, it is unlikely that a single model system could explain the pathophysiology of migraine, a disease considered biologically heterogenous.

New treatment target for medication overuse headache

Bonnet et al. examined nitric oxide (NO)-induced activation of trigeminal neurons in an animal model of medication overuse headache (MOH) induced by triptan. They found an abnormal activation of Nav1.9 channels in meningeal nerve fibers and dural afferent neurons in MOH mice, which subsequently triggers CGRP release, arterial dilation, and mast cell degranulation. The deletion of the *Scn11a* gene, which encodes the voltage-gated sodium channel Nav1.9, abrogates the NO-induced hypersensitivity.[5] Meanwhile, another clinical study showed that

[1] Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2] Brain Research Center and School of Medicine, National Yang-Ming University, Taipei, Taiwan
[3] Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan
[4] Division of Translational Research, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
[5] Department of Neurology, Taipei Veterans, Taiwan General Hospital, Taipei, Taiwan
[6] Faculty of Pharmaceutical Sciences, School of Health Sciences, University of Iceland, Reykjavik, Iceland

Corresponding author:
Kuan-Po Peng, Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany.
Email: k.peng@uke.de

botulinum toxin A in combination with acute withdrawal provides no additional benefit over acute withdrawal alone.[6] Therefore, Nav1.9 channel inhibitors might be a new treatment target for patients with MOH.

Animal model for post-traumatic headache has arrived

The awareness of post-traumatic headache (PTH) has accumulated over the years; however, the underlying mechanisms remain poorly understood. Bree and Levy used a weight-drop device to induce concussion in rats. After the acute phase (by 2 weeks postinjury) of pain hypersensitivity had resolved, the authors could reproduce cephalic pain hypersensitivity by low-dose glyceryl trinitrate (GTN) administration in PTH mice but not in sham animals. This hypersensitivity can be inhibited by the treatment of either sumatriptan or anti-CGRP antibody.[7] This study suggests that PTH might be mediated through a CGRP-dependent mechanism and serves as the first step to PTH-specific treatment options.

Clinical studies and advances in treatment

Role of CGRP in migraine and other headaches: The story goes on

The results of two phase 3 trials of CGRP antagonists (gepants) in the acute treatment of migraine, ubrogepant and rimegepant, have been published. In both randomized controlled trials, gepants were superior to placebo: 2-h pain freedom 19.6% with rimegepant,[1] and 19.2–21.2% with ubrogepant[2]; however, the therapeutic gain (placebo-subtracted value) was low, only 7.6% with rimegepant,[1] and 7.4–9.4% with ubrogepant,[2] compared to the other migraine-specific acute treatment options: 26% with sumatriptan[8] and 12.9–16.9% with lasmiditan (5-HT_{1F} agonist).[9] Nevertheless, no head-to-head comparison has been conducted. It remains a question, whether the effects of both gepants are clinically relevant. Besides, patients either with contraindications for or not responding to triptans were not investigated in gepant studies, and these are the patients who could specifically benefit from them.

CGRP antibodies in treating cluster headache

Two anti-CGRP antibodies have been studied on patients with cluster headache (CH). The study which evaluated the efficacy of fremanezumab for the prevention of episodic CH (NCT02945046) has been terminated early due to the results from a prespecified futility analysis.[10] Conversely, galcalizumab has been shown to be superior to placebo in reducing headache attacks in patients with episodic CH.[11] During weeks 1–3, the patients who received galcanezumab had a mean weekly reduction of 8.7 attacks with a therapeutic gain of 3.5 attacks. At week 3, 71% in the galcanezumab group versus 53% in the placebo group reached at least a 50% reduction in headache frequency.[11] Instead, the placebo-controlled study of galcanezumab in patients with chronic CH did not achieve the primary or secondary endpoints.[12] Newer targets other than CGRP remain to be explored for, the severely disabled, chronic CH patients.

Neuromodulation on patients with chronic CH

In a randomized, sham-controlled, parallel-group, double-blinded study, patients who received the sphenopalatine ganglion (SPG) stimulation were more likely to achieve the primary endpoint, defined as the relief from pain within 15 min (62.5% vs. 38.9%, $p = 0.008$).[13] Among the 45 patients in the SPG stimulation group, nine developed serious adverse events, four of which were implantation related. The SPG stimulation seems efficacious and well tolerated for patients with chronic CH.[13] Unfortunately, the producer of the device has filed bankruptcy and whether the device will be available again remains unknown.

Has the era of personalized medicine in headache disorders finally arrived?

It remains difficult to predict, whether a patient responds to a specific medication, for example, an abortive medication like triptan or a preventive medication like topiramate. Kogelman et al. interviewed 2219 unrelated migraine patients, accessed their acute and prophylactic drugs response, and genotyped all of them and calculated their polygenic risk scores (PRS) for the likelihood of migraine.[14] Among all the medications investigated, the authors found an association between higher PRS, suggestive of a higher risk of migraine, and a positive treatment response to triptan (odds ratio (OR) = 1.25, 95% confidence interval (CI) = 1.05–1.49)) but not other medications. They replicated their findings in an independent cohort comprising 5616 triptan users with an OR of 3.20 (95% CI = 1.26–8.14).[14] This is the first study to show that the response to medication in headache disorders may be genetically determined and the mechanism of how triptan works is closely related to the mechanism behind a migraine generation.

Central or peripheral origin: the debate is everlasting

It has been long debated whether the origin of a migraine attack is central or peripheral. More to the debate, whether certain migraine-specific medications act peripherally or centrally. Sumatriptan has long been considered to act peripherally because of its hydrophilicity and theoretically poor CNS penetration. Deen et al. studied eight patients with a positron emission tomographic scans after the injection of a specific 5-HT_{1B} receptor radiotracer. They found that after sumatriptan administration, the central 5-HT_{1B}

receptor binding in pain-modulating regions was reduced by 16%, suggestive of a binding of sumatriptan to central 5-HT_{1B} receptors.[15] The mechanism, by which it crosses the blood–brain barrier (BBB), is unknown. The finding in this study raises another interesting question: whether the newer generation migraine-specific medications, for example, anti-CGRP or CGRP receptor antibodies, could possibly cross BBB and exert a central action? The theoretical probability of that is considered negligible given an intact BBB; however, some suggested that the BBB might be "leaky" in certain variants of migraine with aura.[16,17] One recent animal study observed a small proportion (0.34%) of anti-CGRP antibodies in central regions like hypothalamus, where an effective BBB is lacking.[18] Future studies are still needed to address whether a central effect of CGRP antibodies is possible.

Potential new treatment target in migraine

ATP-sensitive potassium channels (K_{ATP}) locate downstream in the signaling pathway of either CGRP or NO in triggering migraine. Al-Karagholi et al. investigated whether the opening of K_{ATP} is associated with a migraine attack. In a randomized, double-blind, placebo-controlled, crossover design, among the 16 migraine patients who received the infusion of levcromakalim—a K_{ATP} channel opener, 16 of 16 (100%) developed migraine attacks after levcromakalim compared to 1 of 16 (6%) after placebo.[19] This 100% induction rate is higher than other substances, such as GTN, CGRP, or sildenafil,[19] and therefore, a validation study is warranted. Nevertheless, the study suggests an important role of K_{ATP} in migraine pathophysiology and the blocking of K_{ATP} channel may be a potential target in migraine treatment.

Closing remarks

The articles selected reflect the tremendous contribution from different research groups to improve the treatment of headache disorders and to advance our understanding of their disease pathophysiology. Aside from the CGRP antibodies and antagonist, new potential treatment targets have emerged thanks to the progress made in studies focusing on disease mechanism. Less progress has been made in fields concerning less frequent but disabling headache disorders, for example, chronic CH and facial pain disorders. In sum, it has been a good and fruitful year for headache research, and we look forward to an even brighter future in 2020.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID iDs

Kuan-Po Peng https://orcid.org/0000-0002-2718-3738
Shih-Pin Chen https://orcid.org/0000-0003-3492-9902

References

1. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med* 2019; 381: 142–149.
2. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the treatment of migraine. *N Engl J Med* 2019; 381: 2230–2241.
3. Schain AJ, Melo-Carrillo A, Stratton J, et al. CSD-Induced arterial dilatation and plasma protein extravasation are unaffected by fremanezumab: implications for CGRP's role in migraine with aura. *J Neurosci* 2019; 39: 6001–6011.
4. Melo-Carrillo A, Strassman AM, Nir R-R, et al. Fremanezumab a humanized monoclonal anti-CGRP antibody—inhibits thinly myelinated (Aδ) but not unmyelinated (C) meningeal nociceptors. *J Neurosci* 2017; 37: 10587–10596.
5. Bonnet C, Hao J, Osorio N, et al. Maladaptive activation of Nav1.9 channels by nitric oxide causes triptan-induced medication overuse headache. *Nat Commun* 2019; 10: 4253.
6. Pijpers JA, Kies DA, Louter MA, et al. Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: a double-blind randomized controlled trial. *Brain* 2019; 142: 1203–1214.
7. Bree D and Levy D. Development of CGRP-dependent pain and headache related behaviours in a rat model of concussion: implications for mechanisms of post-traumatic headache. *Cephalalgia* 2018; 38: 246–258.
8. Ferrari MD, Roon KI, Lipton RB, et al. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet Lond Engl* 2001; 358: 1668–1675.
9. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: a phase 3 randomized study. *Neurology* 2018; 91: e2222–e2232.
10. A study to explore the long-term safety and efficacy of TEV-48125 (fremanezumab) for the prevention of cluster headache - full text view - ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT03107052 (accessed 10 December 2019).
11. Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med* 2019; 381: 132–141.
12. Oakes TM, Dodick DW, Goadsby PJ, et al. *61st Annual Scientific Meeting, Phase 3 placebo-controlled study of galcanezumab in patients with chronic cluster headache: results from 3-month double-blind treatment*, 11–14 July 2019, Pennsylvania Convention Center, Philadelphia, PA: American Headache Society.
13. Goadsby PJ, Sahai-Srivastava S, Kezirian EJ, et al. Safety and efficacy of sphenopalatine ganglion stimulation for chronic cluster headache: a double-blind, randomised controlled trial. *Lancet Neurol* 2019; 18: 1081–1090.

14. Kogelman LJA, Esserlind A-L, Francke Christensen A, et al. Migraine polygenic risk score associates with efficacy of migraine-specific drugs. *Neurol Genet* 2019; 5: e364.
15. Deen M, Hougaard A, Hansen HD, et al. Association Between sumatriptan treatment during a migraine attack and central 5-HT1B receptor binding. *JAMA Neurol* 2019; 76: 834–840.
16. Cha Y-H, Millett D, Kane M, et al. Adult-onset hemiplegic migraine with cortical enhancement and oedema. *Cephalalgia* 2007; 27: 1166–1170.
17. Dreier JP, Jurkat-Rott K, Petzold GC, et al. Opening of the blood-brain barrier preceding cortical edema in a severe attack of FHM type II. *Neurology* 2005; 64: 2145–2147.
18. Johnson KW, Morin SM, Wroblewski VJ, et al. Peripheral and central nervous system distribution of the CGRP neutralizing antibody [^{125} I] galcanezumab in male rats. *Cephalalgia* 2019; 39: 1241–1248.
19. Al-Karagholi MA-M, Hansen JM, Guo S, et al. Opening of ATP-sensitive potassium channels causes migraine attacks: a new target for the treatment of migraine. *Brain* 2019; 142: 2644–2654.