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EDITORIAL

Migraine Therapy: Current Approaches and New Horizons

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Primary headache disorders are one of the leading causes of disability globally [1], with in excess of one billion people affected worldwide. The most common biologies that produce this level of disability are that of migraine and cluster headache. While the underlying mechanisms of primary headache disorders remain to be fully characterised, a bench-to-bedside approach to understanding the conditions [2, 3] is beginning to bear fruit in terms of potential novel neurotherapeutics that will revolutionise management and thus reduce disability [4].

Migraine, the most common of the primary headache disorders, is ranked as the 6th most disabling disorder (rising to 3rd in the under 50s age group [5]) globally with a prevalence of up to 15% of the population [1]. It is recognised by the combination of moderate to severe throbbing head pain in a broader context of dysfunctional sensory processing that can manifest as symptoms such as light (photophobia) and sound (phonophobia) sensitivity [6]. As reviewed by Drs. Ong and De Felice [7, 8] in this issue of Neurotherapeutics, the mainstay of current acute attack treatments has been the triptans, serotonin 5-$HT_{1B/1D}$ receptor agonists, which have a well-established efficacy in migraine [9]. Originally developed as cranial vasoconstrictors [10, 11] that has led to small, persistent safety concerns [12], it is now understood that their mechanism of action most likely involves 5-HT_{1D} receptor-mediated modulation of neural transmission independent of their vascular actions. Additional acute therapies and their potential mechanisms including the non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, anti-emetics, corticosteroids and opioids are further discussed.

Interestingly, the triptans demonstrate variable selectivity for the 5-HT_{1F} receptor that is expressed on neurons and not blood vessels and until recently was largely overshadowed in terms of potential migraine therapies. As reviewed by Dr. Vila [13], the identification of a potential 5-HT_{1F} action for the triptans [14] has led to the development of specific 5-HT_{1F} agonists termed the "ditans". Lasmiditan is currently the most advanced molecule that has successfully completed phase III clinical trials for migraine [13] with no indication of any cardiovascular contraindications that limit the utility of the triptans. Similarly, bench-to-bedside approaches identified increased circulating calcitonin gene-related peptide (CGRP) levels in animal and human experimental migraine models as well as during spontaneous attacks [15–17]. As such, CGRP has emerged as a key neuropeptide target for migraine therapy. The initial attempts to develop small molecule antagonists for the CGRP receptor "gepants" are documented in the review of Drs. Holland and Goadsby [18], from the initial positive results with Olcegepant [19] to the detrimental identification of potential hepatotoxicity following their testing for migraine prophylaxis. Despite this off-target class effect on liver enzymes, two small molecule antagonists, Ubrogepant and Rimegepant, remain in development for acute migraine therapy.

When migraine occurs frequently, combined with the risk of medication overuse headache due to excessive use of acute medications, then prophylactic therapeutics are the preferred choice. The current options for migraine prophylaxis are described by Drs. Sprenger, Viana and Tassorelli [20]. As noted, the majority of prophylactic treatments are adopted from alternate indications, including propranolol (β-blocker), amitriptyline (antidepressant), valproate and topiramate (both anticonvulsants). Unfortunately, current prophylactic therapies can suffer from a lack of specificity, poor tolerability, potential side effects and limited efficacy, leading to dissatisfaction in a large proportion of patients [21]. On a more positive note and borne from the clinical success of the gepant small molecule CGRP receptor antagonists, several monoclonal antibodies (mAbs) have been developed that target either CGRP or its receptor. As reviewed by Drs. Raffaelli and Reuter, all phase III clinical trials for CGRP targeted mABs "umabs" have

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proven successful with first to market compounds eagerly awaited.

In parallel to the development of novel therapeutics for migraine, there is a growing literature on the use of neuromodulatory approaches. These non-pharmacological approaches are reviewed by Drs. Puledda and Shields [22] and represent an ever-increasing area of clinical practice. As noted, when confronted with patients who are unwilling to accept possible drug-induced adverse events, clinicians should be aware of the array of treatment strategies ranging from nutraceuticals to neurostimulation techniques such as vagal nerve and transcranial magnetic stimulation.

On the rarer spectrum of primary headaches, cluster headache, paroxysmal hemicrania, hemicrania continua and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNCT) form a group of headaches termed the trigeminal-autonomic cephlalgias (TACs). Their presumed pathophysiological basis resulting from trigeminal-autonomic reflex is discussed by Drs. Wei and Jensen [23], highlighting the significant translational research [24, 25] that has led to new therapies, including oxygen and neurostimulation approaches. There is much hope that current novel therapeutics such as those targeting CGRP signalling and 5-HT_{1F} receptors will further show benefit in TACs with several clinical trials ongoing.

Building on the recent success of novel therapeutic and non-pharmacological approaches for migraine and TACs, a number of key targets have been proposed that remain to be fully characterised. The most promising of which are reviewed in the current issue of Neurotherapeutics. Drs. Hoffmann and Charles [26] tackle the potential therapeutic modulation of glutamatergic signalling that, akin to CGRP, is elevated during migraine attacks, and is genetically associated with rare monogenic forms of migraine. At least for metabotropic glutamate receptor 5 blockers, there is positive double-blind, parallel group, clinical trial data. Drs. Vollesen, Amin and Ashina further highlight the significant potential of targeted modulation of pituitary adenylate cyclase-activating peptide (PACAP) [27]. PACAP levels fluctuate across migraines and vary between migraineurs and controls. In agreement with a role for PACAP, experimental data highlight the utility of targeting the specific PAC_1 receptor over the less specific $VPAC_1$ and $VPAC_2$ receptors [28]. Borne from the previous demonstration of targeting both CGRP and its receptor, both PAC_1 receptor blockers and mAbs targeting PACAP itself have been proposed with phase II clinical trials planned. Interestingly, PACAP signalling is linked to several hypothalamic functions including the regulation of circadian rhythms that have been recently linked to migraines [29]. This forms part of a growing evidence base for the role of the hypothalamus in the pathophysiology of migraines and TACs [2, 30]. While several hypothalamic neuropeptides have been proposed to show clinical promise, the orexins, as reviewed by Drs. Strother, Srikiatkhachorn and Supronsinchai [31], have demonstrated clear preclinical impact [32, 33]. Unfortunately, a single clinical trial exploring a dual orexin receptor antagonist failed to show any effect in migraine prophylaxis [34]; however, several limitations likely explain this negative result. In conjunction with orexinergic research, the hypothalamic oxytocin, PACAP and Neuropeptide Y pathways along with their clinical potential are discussed.

One key mechanism that remains under investigation is the inhibition of nitric oxide synthase. As reviewed by Drs. Pradhan, Bertels and Akerman [35], the nitric oxide (NO) donor nitroglycerin is the most widely used human experimental trigger for migraine, while several members of the NO signalling cascade are upregulated in migraine. As such, broad-spectrum NOS inhibitors have shown some promise in clinical trials. While specific inducible (iNOS) and endothelial (eNOS) inhibitors have demonstrated variable efficacy, the utility of neuronal (nNOS) inhibitors remains the most promising target. The final review in the current issue by Drs. Karsan and Dussor [36] focuses on the potential role of acid-sensing ion channels (ASICs) in migraine therapy. Given their sensitivity to fluctuating pH levels and proposed roles in several neurological conditions including stroke and epilepsy, they have emerged as key targets for migraine and pain more generally. Of the four subunits, ASIC1 (central nervous system-enriched) and ASIC3 (peripheral nervous system-enriched) demonstrate the most potential currently, with bench-to-bedside approaches demonstrating preclinical efficacy for their modulation [37, 38], combined with a small open-label clinical observation showing that the broad-spectrum ASIC blocker amiloride has potential clinical efficacy in migraine with aura [37].

While the above areas of success reviewed in this issue of Neurotherapeutics hint towards the growing optimism for the future pharmacological and non-pharmacological treatment of primary headaches, there have been some notable cautionary tales. Approaches that have failed, such as substance P/neurokinin-1 receptor antagonists [39], or targeting neurogenic dural inflammation as developed in experimental animals [40], are equally lessons in neurotherapeutics skewed by uninformative laboratory models. What stands out as the headache field moves forward in the pursuit of novel targeted safe therapeutic treatments is that neural targets are sufficient, effective and clearly offer a safety advantage over vascular targets for which there is no longer any purpose in pursuing [41].

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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