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REVIEW ARTICLE

Some aspects on the pathophysiology of migraine and a review of device therapies for migraine and cluster headache

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Abstract
Migraine is a common, severe disease, affecting the brain and blood vessels, causing much pain, time missed from work and family, and severe disability. It affects approximately 12% of most Western populations studied and affects women three times more than men. Cluster headache is a much less common dysfunction of the hypothalamus, involving the sphenopalatine ganglion and other areas; it causes more frequent, shorter, and even more intense pain than migraine. The pain usually comes in cycles and is associated with ipsilateral autonomic features and associated with irritability and inability to stay still. It affects less than 0.1% of the population and is slightly more prevalent in men than women. Although we have some acute care and preventive medications for both types of headache, no treatment is optimal for each patient and some will not respond well or have significant adverse events to existing therapies.

Keywords CGRP · Monoclonal antibodies to calcitonin gene–related peptide or its receptor · Headache devices · Migraine therapy · Cluster headache therapy · Pathophysiology of migraine

Introduction

We are always looking for acute care medications that work faster, more completely with fewer adverse events. The five preventive medications approved by the FDA for migraine have been somewhat effective; but due to lack of optimal efficacy and troubling side effects, fewer than 20% of patients remain on a preventive treatment at the end of 1 year.

In May 2018, the FDA approved the first of four monoclonal antibodies to CGRP (calcitonin gene–related peptide) or its receptor as novel preventive treatments for migraine and possibly cluster headache will follow this year. The translational road from early basic research on CGRP and its effect on blood vessels to effective migraine prevention and acute care has been a long and exciting one. Once it became clear that CGRP was an important target, several companies have been developing both monoclonal antibodies to CGRP and its receptor as well as gepants, small molecule CGRP receptor antagonists, both for acute care and prevention of migraine. Herein, we describe the steps that led from discovery to the development of CGRP-related headache therapies.

Then we will describe and show the latest data for eight devices for acute care and/or prevention of migraine and cluster headache. One works with a triptan, but most stimulate the brain, cranial nerves, or specific peripheral nerves.

Some aspects on the pathophysiology of migraine

Migraine is a painful, debilitating neurological disease, having a huge impact on individual and public health. In a survey about years lived with disability, migraine was recently ranked in second place. Although evidence suggest no increase in migraine prevalence in a 10-year period, the cumulative lifetime incidence is very high (43% in women, 18% in men), affecting especially young adults. Migraine may occur in single attacks but sometimes it becomes more frequent and is called frequent episodic or chronic migraine. The latter is

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defined as having headaches 15 or more days per month, which causes a marked impact on patients and their families.

While single attacks may respond to triptans, preventive treatments are needed in frequent episodic or chronic forms of migraine. Most of the currently available preventives show at best modest effects but are associated with considerable adverse events and none were developed specifically for migraine. Therefore, we need new, disease-specific, preventive treatments for migraine which are effective, well-tolerated, and easy to use.

Great progress has been made in understanding the pathophysiology of migraine. However, there are still some questions regarding the origin of migraine pain and its chronification.

No single undisputed hypothesis yet exists regarding the mechanisms behind primary headaches. The major hypotheses of the underlying migraine mechanisms are currently in question: is migraine a purely vascular or neurologic disease, or does it involve both mechanisms as a neurovascular disorder. Although the pathogenesis of primary headaches is still unclear, it likely involves the first branch of the trigeminal nerve (the trigeminovascular system) connecting nociceptors and the meninges in the periphery to their central terminations in the brain stem (CNS). The CNS itself is devoid of nociceptors, but the intracranial blood vessels are supplied with sensory nerves and receptors that may respond to thermal and mechanical stimuli. It is often suggested that the starting point in a migraine attack, at least in the aura phase, is a cortical wave of spreading depression (CSD) which is associated with local release of various molecules that can have effects on neurons, glial cells, and vessels [1]. These mediators were suggested to diffuse to the overlying leptomeninges and activate vascular nociceptors. Thus, the sensory nerve fibers around cranial blood vessels are likely to play an important role in head pain of a migraine attack. As an important link in the process, knowledge of the CNS connections of the sensory nerves is essential for understanding primary headache-associated intracranial and referred pain. Detailed transganglionic neuronal tracing has been carried out from extra and intracranial blood vessels to further our knowledge of the central connections of the trigeminovascular nerves (TVN), which show differential somatotopic expression in the trigeminal nucleus caudalis (TNC) [2].

Today, the prevailing hypothesis proposes that migraine pain originates from a central mechanism that starts in the hypothalamus (already in the premonitory phase) that during the actual attack involves the brainstem regions and finally the TVN [3]. Depending on the severity, there is a differential degree of both central and peripheral sensitization which accounts for much of the symptomatology, thus underscoring a crucial role of trigeminal perivascular nociceptive afferents. The dural afferents might be activated further during dural exposure to inflammatory substances or when dural mast cells are degranulated. The trigeminal ganglion provides a key site accessible to drugs in the circulation because it lacks a blood-brain barrier [4]. Both new and old antimigraine drugs may act here to reduce the headache [2].

Discovery of CGRP in relation to migraine

Early studies on the distribution of the calcitonin gene (CT) revealed that it is differentially regulated and expressed as calcitonin gene–related peptide (CGRP) in neuronal tissues [5]. This excited our group and we produced CGRP for in vitro and in vivo studies, and for immunization to produce antibodies to use in quantitative radioimmunoassay and for localization studies with immunohistochemistry. The first data were presented in a CNRS meeting in Paris 1984 on Regulatory Peptides and later in a series of publications [6–8]. Many of the trigeminal ganglion neurons (50%) contain CGRP that partially co-localized substance P. Lesioning of the trigeminal ganglion resulted in the absence of CGRP positive fibers from intracranial arteries [7]. Subsequent tracing studies from intra and extracranial arteries revealed that the sensory CGRP positive fibers originate in the trigeminal neurons [9–11]. Functional studies showed that CGRP was a very potent vasodilator of cerebral arteries and arterioles, activating adenylyl cyclase in the smooth muscle cells and being independent of the endothelium [6]. In vivo, the CGRP potently relaxed cortical arterioles but not venules [12]. Denervation (removal of perivascular sensory CGRP) did not modify resting cerebral blood flow or any of its fundamental regulation mechanisms; however, the trigeminovascular reflex was demonstrated [12]. CGRP in the trigeminal sensory fibers turned out to be a key messenger to reverse induced local vasoconstriction and to dilate the vessel back to original tone, but it is inactive upon local application on relaxed vessels. Later experiments using CGRP blockers showed no tonic effects per se of e.g., gepants or monoclonal antibodies. It is likely that the system needs to be activated to demonstrate an effect [12].

The finding was suggested to be important for brain blood flow (CBF) to remain constant and involved in migraine pathophysiology [8]. The decisive results for demonstration of its involvement in primary headaches appeared a few years later demonstrating that CGRP was the only neuronal messenger that associated with the headache in migraine and cluster headache [13–15].

Pharmacology of CGRP antibodies

Small molecule CGRP receptor antagonists (gepants) have been shown to effectively abort acute attacks of migraine headache [16]; however, there is a need for new preventive therapies in frequent episodic migraine and in chronic migraine. Antibodies binding to CGRP have been around in many laboratories ever since CGRP was discovered more than

three decades ago; but their use in therapeutics has a much shorter history. The use of monoclonal antibodies has shown effectiveness against CGRP; but due to their large size, they do not pass across the blood-brain barrier [17, 18]. They can inhibit neurogenic vasodilation in dura and skin without an effect on the heart rate and blood pressure of the rat [19]. These results suggest that CGRP function-blocking antibodies may be useful for the preventive treatment of migraine: a single dose provides slow onset but long-lasting effect. In these experiments in particular, two clones of antibodies were studied that bind to a C-terminal epitope of CGRP (muMab 7E9 with the highest affinity to human αCGRP) [20]. In the hind paw of the rat, local blood flow increase was blocked by the anti-CGRP antibody [19]. Thus, the antibodies may have general effects.

CGRP exists in the circulation in two forms; αCGRP and βCGRP isoforms with minor differences in pharmacological activity but with differential origin, neuronal versus mainly gastrointestinal origin, respectively. At present, four monoclonal antibodies exist for migraine prevention, three against the CGRP ligand and one against the CGRP receptor. Clinical trials have revealed efficacy and very few adverse effects. The advantage of the antibody approach is their long duration of action and high specificity allowing for monthly or quarterly dosing and highly selective targeting. The three monoclonal antibodies against the CGRP ligand are fully humanized and potently and selectively bind to CGRP; however, they are not specific for any of the CGRP isoforms or origin of the peptide (eptinezumab, fremanezumab, and galcanezumab) [2]. Available preclinical data for fremanezumab, an IgG2a antibody, show binding to CGRP and detail its functional consequences on CGRP signaling. In human arteries, fremanezumab in clinical doses reduces the maximum relaxant response to CGRP, by binding to the peptide and thereby reducing available CGRP to the post-synaptic receptor. Erenumab is a fully human CGRP immunoglobulin G2 (IgG2) monoclonal antibody constructed against the N-terminal of the two CGRP receptor elements CLR (calcitonin receptor-like receptor) and RAMP1 (receptor activity modifying peptide 1) [2]. These two components form the CGRP receptor and erenumab binds to both, which forms the high selectivity.

Recent studies on human intracranial arteries show blockade of the CGRP effects by reduced maximum without inhibition of other vasodilators. These antibodies have all the overarching goal of reducing the CGRP activity and thereby preventing the migraine attack; all the available trials have confirmed this hypothesis.

Presently, three of these antibodies are on the market in the USA (eptinezumab is not yet approved by the FDA) and are being introduced within the EU, Australia, and probably elsewhere in the near future. Preliminary reports suggest good efficacy, rapid onset of effect, no contraindications, and few AEs in the general population. It is quite rewarding to follow the path from the original findings to the clinic and observing the positive reports from our patients.

Device therapies for migraine and cluster headache

Now that we have read about the importance of blocking CGRP and the gepants and four antibodies that accomplish that, we will turn to devices to treat migraine and cluster headache. Herein, we present the latest data on eight devices that are recently available or soon to be approved by the FDA. One stimulates the brain with a magnetic pulse; several stimulate peripheral or cranial nerves with electrical pulses and one works as a novel skin device to introduce a triptan into the circulation. Other devices exist or may soon be approved and you can read more about them and these below in an article published for last year's ANIRCEF conference [21].

Single pulse transcranial magnetic stimulation (sTMS)

Single pulse Transcranial Magnetic Stimulation was first studied for the acute care of migraine with aura in a randomized, controlled trial vs sham stimulation. The 2-h pain free rate was 39% vs 22% for sham. The device was then studied and shown to work acutely on migraine without aura and also prevention of migraine when used several times per day. It is approved in Europe and the USA for those three types of headache treatment. Studies have shown that total migraine freedom at 2 h was 26% which was comparable to some triptans, but only comparing with historical data, not in a head to head study. The prevention studies have shown the 50% responder rate to be 45% for completed cases vs 20% for the sham. Other trials have been compared to a derived factor not a sham or have been open, showing a mean reduction in headache days compared to baseline [22]. The current model is named the sTMS Mini and can be rented on a monthly basis after it is prescribed by a physician.

Transcutaneous supraorbital nerve stimulation (tSNS)

This device stimulates the supraorbital and supratrochlear nerves bilaterally and is approved in the USA and Europe for both acute care and prevention of migraine. These four nerves in the forehead are end branches of the frontal nerves which come off the ophthalmic division of the trigeminal nerve. It first gained FDA approval for prevention of migraine but caused significant bilateral frontal paresthesias which bothered some patients. After its approval, it was noted that some patients used it for acute care of migraine on their own, so a study was performed showing its effectiveness. The primary endpoint was the mean change in pain intensity at 1 h

compared to baseline as seen on a visual analog scale in 99 patients. Although both the verum and the sham stimulation worked, the verum was superior with a decrease of 59% in pain levels versus 30% for the sham [23].

There are three versions of the device, named Cefaly, which are now smaller than the originals and may cause fewer paresthesias. One is for acute care, one for prevention, and one can work for both. The device can be bought after it is prescribed by a physician.

Remote modulation device for the upper arm using CPM (conditioned pain modulation)

A novel, remote, neuromodulation device is worn on the upper arm and blocks migraine pain acutely by conditioned pain modulation (CPM). A peripheral nerve stimulation of the median and musculocutaneous nerves sends a subclinical painful signal to the thalamus and activates the descending pain inhibitory pathway. The device from Israel, named Nerivio Migra, was studied in a prospective, randomized, double-blind, sham-controlled, multicenter study in Israel and the USA. The study was conducted on 252 adults from 18 to 75 years of age, who either received the verum or sham stimulation. The 2-h pain relief rate was 66.7% for the device versus 38.8% for the sham. Pain freedom at 2 h was 37.4% and 18.4% respectively. Both were strongly statistically positive, as was the 48-h sustained pain-free and pain-relief response. There were very few adverse events, the most common being sensation of warmth in 1.6% of patients stimulated. In a post-hoc analysis of this study, the efficacy appears to be equivalent to triptans and superior to NSAIDs. This treatment will be used at home and few adverse events are expected. It will be sold and should not be very expensive. The first publication about this device was by Yarnitsky in 2017 [24] and new ones are in press.

Combined occipital and trigeminal neuromodulation

The Relivion is a device which delivers both bilateral occipital and supraorbital trigeminal nerve stimulation. These occipital nerves conduct the signals directly into the brainstem via C2 and C3. The supraorbital nerves conduct the stimulus via the ophthalmic branch of the trigeminal nerve. In a randomized, double-blind, sham-controlled clinical trial with an $n = 55$ performed by Dr. Oved Daniel at a single center in Netanya, Israel, headache relief at 2-h post stimulation was 76.2% for the device versus 31.6% for sham. Pain freedom at 2 h was 41.7% versus 20% for the sham. Approval is expected by the second quarter of 2019.

Caloric vestibular stimulation (CVS)

A solid-state system enables caloric vestibular stimulation bilaterally without producing significant adverse events. The stimulation, through an earphone type apparatus, which gives caloric stimulation to both external auditory canals, connects with the trigeminal fibers in the brain stem to interfere with the migraine process by downregulating central migraine mechanisms. Via a fluctuating thermal stimulation, headache prevention occurs without causing the typical nausea and vertigo of bilateral cold water caloric stimulation. In a randomized, double-blind, clinical trial, the intention-to-treat analysis showed a 2.3 headache day decrease per month for the active versus sham with a p value = 0.02. Device-related adverse events were similar to placebo and consisted of nausea, dizziness, ear discomfort, etc. The device is already approved by the FDA and should be available by the fourth quarter of 2019 [25].

Sphenopalatine ganglion stimulation for the acute care of chronic cluster headache

The sphenopalatine ganglion, sitting in the pterygopalatine fossa behind the nose, is a cross roads of sympathetic and parasympathetic fibers with connections from the maxillary division of the trigeminal nerve that has long been known to play a crucial role in cluster headache. Many interventional techniques to disrupt or disable this structure or its connections have helped to a limited extent over many years. This novel device is a microstimulator, designed to fit the facial anatomy, and is introduced under general anesthesia via the oral route and placed on the sphenopalatine ganglion and tacked into place on the bone. There are no wires to break or move or batteries to run out of power; stimulation is applied by a wireless remote controller placed on the cheek. Each headache in patients with chronic cluster is acutely treated as soon as it starts.

The results from the US pivotal CH-2 study of acute pain relief in 992 attacks in chronic cluster headache show a positive response in 62% of patients with active stimulation and 39% with an active control. This control sham caused low-grade stimulation to the second division of the trigeminal nerve in the cheek and actually worked at a low level, raising the placebo response rate. In spite of this, the p value = 0.008. For pain freedom at 15 min, 40% of patients qualified versus only 23% of controls, with $p = 0.04$. The 50% responder analysis for pain relief at 15 min was 63% versus 29% for the active control, $p = 0.03$.

The reduction in chronic cluster burden decreased from a baseline median attack rate of 34 per month to 9 attacks per month, a reduction of 72%. Triptan use was reduced from 3.7 injections of sumatriptan per week to 1.2 [26]. The device named Pulsante may be approved by the fourth quarter of 2019.

The non-invasive vagal nerve stimulator

A hand held, patient-controlled device placed over the vagus nerve on either side of the anterior-lateral neck, named the gammaCore, preferentially stimulates the afferent A and larger B fibers, not the C fibers which mediate bradycardia and bronchoconstriction. There are multiple mechanisms of action including inhibition of cortical spreading depression, decrease in CNS glutamate, suppression of neuronal firing in the trigeminal cervical complex, and modulation of the trigeminal autonomic reflex. GammaCore has received a CE Mark in Europe and FDA approval for acute care of migraine and cluster headache, and recently, adjunctive care in the prevention of cluster headache.

In the Presto study on episodic migraine, active stimulation was superior to sham at 30 and 60 min but not at 120 min, which was the primary endpoint. The 50% responder rate for pain relief at 120 min was 47.6% for active stimulation versus 32.3% for the sham, with a p value of 0.026. The 50% responder rate for pain freedom at 2 h was 32.4% versus 18.2% for the sham, $p = 0.02$ [27].

The Preva study for the prevention of cluster headache treated 114 patients twice daily and prn for rescue. All patients had 2 weeks of standard of care treatment and then went into the active phase for 4 weeks, in which half also received active stimulation in addition versus sham. They then all went into a 4-week open trial and received both standard of care treatment plus active stimulation. The number of cluster headache attacks per week in the active stimulation group dropped from 15.9 to 9, a drop of 6.9 attacks with a p value of 0.0025. Those patients who received only standard of care dropped from 16.6 attacks per week to 14.6 attacks, a drop of only 2 headaches per week [28].

Microneedle zolmitriptan transdermal patch (ADAM)

A novel transdermal patch containing microneedles impregnated with zolmitriptan is named ADAM, the adhesive dermally applied microneedle system. It allows for the rapid and consistent dissolution of medication into the capillary bed. The shallow depth of penetration of the proprietary micro projections into the superficial skin layers, and not the subcutaneous space, minimizes stimulation of nerve endings and results in a pressure feeling, not pain. The patch is the size of a US quarter and is applied with a simple device that standardizes the application pressure. It is worn for 30 min on the upper arm and then discarded.

A phase 1 trial of two of the 1.9 mg patches of zolmitriptan (total of 3.8 mg) shows a steep rise of the plasma concentration of the patches compared to a 2.5-mg tablet. The Cmax of the patch was 13 ng/ml compared to 3 ng/ml of the 2.5-mg tablet of zolmitriptan. In a phase 3 trial of the 2 patches, successful achievement of both co-primary endpoints was realized. Pain freedom at 2 h was 41.5% for the active patch and 14.3% for placebo, with an impressive p value of 0.0001. Freedom from most bothersome symptom was also strongly positive [29]. A safety trial is ongoing and application to the FDA for approval may occur in early 2020.

Conclusions

Three of the four monoclonal antibodies to CGRP or its receptor are now available in the USA and some other countries. The fourth type is undergoing FDA review. These will all be used as migraine preventives and two are hoping for approval of cluster headache prevention. Several small molecule CGRP receptor antagonists (gepants) should be improved in the next 2 years for acute care and prevention of migraine. Multiple devices, mostly without, but also with medication, some stimulating peripheral or cranial nerves and another stimulating the cortex with magnetic pulses are either available or will be soon. Headache specialists need all the new therapies they can get that are effective, easy to use, with few adverse events. Some patient will prefer an effective, easy to use device to medications.

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