

## NEW MOLECULES IN MIGRAINE TREATMENT

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### Abstract

In the 1990s, serotonin receptor agonist 5-HT<sub>1B/1D</sub> (the triptans) became available on the market for migraine treatment. Although the triptans are highly effective in aborting migraine attacks, the vasoconstrictor effect in cerebral and coronary territory limits their use. In the “post-triptans” era, new molecules, without vasoactive components are about to expand migraine treatment *armamentarium*, such as: serotonin 5-HT<sub>1F</sub> receptor agonists, calcitonin gene related peptide (CGRP) receptor antagonists (olcegepant, telcagepant) and monoclonal antibodies (mAbs) targeting the CGRP, glutamate receptor (AMPA/kainate) antagonists, transient receptor potential vanilloid (TRV1) antagonists, nitric oxide (NO) synthesis inhibitors, prostanoid E4 receptor antagonists.

### Rezumat

În anii 1990, au apărut pe piața farmaceutică agoniștii receptorilor serotonininei 5-HT<sub>1B/1D</sub> (triptanii) pentru tratamentul atacurilor migrenoase. Deși triptanii sunt foarte eficienți în atacurile migrenoase, folosirea lor este limitată de efectul vasoconstrictor din teritoriul cerebral și coronarian. În era „post-triptani”, noi molecule, fără componente vasoactive, sunt pe cale să completeze *armamentarium*-ul pentru tratamentul migrenei, precum: agoniștii de receptori 5-HT<sub>1F</sub>, antagoniștii receptorilor CGRP și anticorpii monoclonali anti-CGRP, antagoniștii receptorilor de glutamat (AMPA/kainate), antagoniști ai TRV1, inhibitori ai sintezei de NO, antagoniști ai receptorilor prostanoid E3.

**Keywords:** migraine, triptans, new molecules, neural targets

### Introduction

Migraine is highly prevalent worldwide, affecting 11 % of the population, being a public health problem [2]. Migraine is a brain disorder, with a complex neurobiology, and so research must be oriented to find new neural targets and new molecules for its treatment.

Migraine is characterized by recurrent episodes of severe unilateral throbbing headache, associated with autonomic nervous system dysfunction (nausea, vomiting) and with sensitivity to light, sound and head movement (migraine without aura) [1]. About one third of migraineurs experience fully reversible neurological symptoms. The aura is characterized by transitory visual or sensory-motor dysfunction that precedes or accompanies the headache (migraine with aura) [1]. Chronic migraine - a new concept introduced by the International Classification of Headache Disorders 3<sup>rd</sup> edition, is defined as headache on more than 15 days *per* month, for at least 3 consecutive months, the headache having the clinical features of migraine without aura for at least 8 days per month [1]. Chronic migraine produces an important disability to the patients, its treatment being more challenging than for episodic migraine. Topiramate

and onabotulinumtoxin A are the two drugs recommended in chronic migraine. Frequently, chronic migraine is associated with medication-overuse-headache.

### Current therapies for migraine

For acute migraine treatment, current guidelines recommend non-specific molecules such as NSAIDs (non-steroidal anti-inflammatory drugs), acetaminophen and aspirin, in patients with mild to moderate attacks. They are effective in some patients, but with the cost of gastrointestinal effects [3]. NSAIDs must be used with caution, the regular intake of one or more NSAIDs on  $\geq 15$  days per month, for  $> 3$  months can induce medication-overuse headache (MOH) [1].

Antiemetic drugs (metoclopramide, domperidone) may be associated to NSAIDs to treat vegetative symptoms (nausea, vomiting) associated to the headache and also to improve analgesics resorption [3]. Due to their addictive potential and the risk of medication overuse headache, opioids must be used only in selective cases [3].

Specific anti-migraine drugs (ergot alkaloids, triptans) are indicated to abort moderate-to severe headache attacks [3].

If there is a high frequency or a great severity of migraine attacks, un-responsivity to acute drug treatment, or long and disabling auras, there is need for a prophylactic treatment of migraine. According to the guidelines, molecules used in migraine preventive treatment are beta-blockers (metoprolol, propranolol), calcium-channel blockers (flunarizine – in familial hemiplegic migraine), anti-epileptic drugs (valproic acid, topiramate), and antidepressants (tricyclic – amitriptyline, selective serotonin reuptake inhibitors (SSRIs) – fluoxetine) [3]. Migraine may be comorbid with other neurological and psychiatric disorders, including stroke, epilepsy, depression and anxiety disorders, treatment must be selected also according to these aspects.

#### ◆ Serotonin receptor agonists

Serotonin (5-Hydroxytryptamine, 5-HT) is a basic amine derived from tryptophan, which is involved in migraine pathogenesis. During migraine attacks there is an increased urinary excretion of the 5-hydroxyindoleacetic acid (5-HIAA - the main metabolite of serotonin) [4] and in the meantime a drop of the platelet 5-HT [5]. So, in migraineurs, there are increased plasma 5-HT levels during the attack and reduced interictal levels [6, 7].

5-HT receptors have different molecular structures: guanine nucleotide G protein-coupled receptors, ligand-gated ion channels and transporters. In humans, there are at least five 5-HT<sub>1</sub> receptor subtypes: 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1C</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub>, and 5-HT<sub>1F</sub>.

Humphrey et al [6, 7] clarified the 5-HT receptors responsible for selective cranial vasoconstriction. The small meningeal vessels contain mainly 5-HT<sub>1B</sub> receptors, whereas the trigeminal ganglion and free trigeminal nerve fibres contain mainly 5-HT<sub>1D</sub> receptors. 5-HT<sub>1B</sub> receptors mediate vasoconstriction in cerebral and coronary arteries, whereas 5-HT<sub>1D</sub> receptors are involved in neurogenic inflammation of the *dura mater*.

Ergot alkaloids (ergotamine, dihydroergotamine - DHE) represent the first class of specific anti-migraine drugs. They act as 5-HT receptors agonists, but they also bind  $\alpha$ -adrenoceptors and dopamine receptors. They have low oral bioavailability and many side effects (nausea, vomiting, paraesthesia, ergotism), causing also vasoconstriction at the coronary, cerebral and peripheral level.

Ergot alkaloids are contraindicated in cardiovascular, cerebrovascular diseases, Reynaud's syndrome, pregnancy, uncontrolled arterial hypertension, renal and liver failure. Ergotamine - overuse headache may appear in the case of regular intake for  $\geq 10$  days per month, for  $> 3$  months [1]. Ergot alkaloids use decreased after triptans appearance, but they are still indicated in very long

and severe headache attacks, or in the case of headache recurrence after triptans (exploiting their long half-time and low headache recurrence rate) [3]. For these old drugs, a new device for the delivery of DHE by oral inhalation (in order to increase the pulmonary distribution and systemic absorption) was recently approved by FDA (Levadox<sup>®</sup>).

In the early 1990s, a new class of anti-migraine drugs - selective 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors agonists (triptans) for the acute treatment of migraine was developed.

Migraine's headache might be due to sterile, neurogenic inflammation in the cranial arterial walls. The trigeminal-vascular system concept referred to the pain-producing intracranial structures (large cerebral vessels, pial vessels, large venous sinuses and *dura mater*) that are surrounded by unmyelinated fibres that arise from the trigeminal ganglion.

The pain information from cranial structures is directed orthodromic from vessels walls to trigeminal *nucleus caudalis*, ascends centrally in the quinto-talamic tract, than synapse in contralateral thalamus and then projects to the cortex.

There is also an antidromic pathway, namely neurons from the trigeminal ganglion release substance P, calcitonin-gene-related peptide (CGRP), that are conducted by trigeminal nerve fibres towards arterial wall. These molecules determine vasodilatation, plasma extravasation and enhance neurogenic inflammation from cranial vessels [8].

The inflammation from the vessel wall sends pain information back to the trigeminal ganglion, which releases inflammatory molecules (antidromic CGRP, substance P).

In time, this vicious cycle determines central sensitization of the trigeminal ganglion, having the clinical correspondent of cutaneous allodynia (abnormal perception of pain from a normally non-painful mechanical or thermal stimulus) in "transformed" migraine.

Triptans act by inhibiting the peripheral trigeminovascular neurons and also act centrally along the trigeminal nociceptive pathways.

The first molecule of this class of drugs was sumatriptan. Other triptans emerged immediately after, rising a SO CALLED „triptan war”: zolmitriptan, rizatriptan, naratriptan, eletriptan, almotriptan, frovatriptan.

In case of headache recurrence (worsening of headache after pain free state achieved with a drug within 24 hours), a second dose of triptan is effective in most cases. If one triptan fails in acute migraine attack, another must be tried. Early triptan treatment in migraineurs may prevent the central sensitization.

The general contraindications for the use of triptans are: arterial hypertension (untreated), coronary

heart disease, cerebrovascular disease, Raynaud's disease, pregnancy and lactation, severe liver or kidney failure, age under 18 (except sumatriptan nasal spray) and age above 65 [3]. Also, there is a risk of medication-overuse headache in the case of triptan intake for  $\geq 10$  days per month, for  $>3$  months [1].

The development of the triptans largely improved the *armamentarium* for the acute treatment of migraine. However, many migraineurs do not respond optimally to triptans and patients with cardiovascular co-morbidities can't use triptans.

Shortcomings of the triptans have prompted research on novel serotonergic targets for migraine treatment, to find more selective agonists which will be safer, without the 5-HT<sub>1B</sub> mediated vasoconstriction effect.

- **The 5-HT<sub>1D</sub> receptor agonists** determine inhibition of dural neurogenic protein plasma extravasation, without vasoconstrictor effects. PNU-142633 (5-HT<sub>1D</sub> receptor agonist) has a lower potency compared to sumatriptan, a poor blood-brain barrier penetration; it proved ineffective in clinical trials [9].

- **The 5-HT<sub>1F</sub> receptor** is distributed in the trigeminal ganglion and the trigeminal *nucleus caudalis*. Experimentally, in neural tissue, 5-HT<sub>1F</sub> receptor agonists blocked neurogenic inflammation and c-Fos expression (a marker of neuronal activation), without evidence of vasoconstriction in vascular tissue models *in vitro*.

The 5-HT<sub>1F</sub> agonists act by hyperpolarizing nerve terminals and thereby inhibiting trigeminal impulses. Two "ditans" (selective 5-HT<sub>1F</sub> agonists) were tested in human trials for migraine. Both molecules were as efficient as 100 mg oral sumatriptan in treating migraine attacks.

LY-334370 was effective in acute migraine; the adverse events were different from triptans (dizziness, fatigue, somnolence, and paraesthesia). The project was stopped due to the proven liver toxicity in dogs [10].

Lasmiditan (COL-144, LY573144) is a 5-HT<sub>1F</sub> agonist administered orally, supported by a positive dose-ranging phase II, *placebo*-controlled trial [11]. Opposite to triptans, Lasmiditan has a good central penetration, so its side effects are from the central nervous system area (dizziness, paraesthesia and vertigo – due to activation of cerebellar 5-HT<sub>1F</sub> receptors), no vasoactive effects and no changes in the electrocardiography parameters were found consequent to its administrations.

The 5-HT<sub>1F</sub> receptor agonists are now considered a new class of molecules – termed "neurally acting anti-migraine agents" – having a non-vascular mechanism for the treatment of migraine attacks [13]. The serotonergic system acts in connection with the glutamatergic one as well as the CGRP-ergic systems.

#### ◆ **CGRP ("Calcitonin Gene-Related Peptide") and migraine**

Calcitonin gene-related peptide (CGRP) is an ubiquitous neuropeptide involved in migraine occurrence. CGRP receptors are found in meningeal blood vessels, trigeminal ganglion, and in the periaqueductal grey matter [14].

CGRP is released by the trigeminal sensory neurons. CGRP is significantly elevated in the external jugular veins of patients, during migraine attacks [8].

Having CGRP as neural target basis, 2 new types of molecules were developed for migraine treatment: the CGRP receptor antagonists (blockers) – the "gepants" (CGRP-Ras), that compete for binding sites with endogenous CGRP, reducing its vasoconstrictive properties, and the monoclonal antibodies (mAbs) targeting the CGRP, that binds to CGRP and neutralize its effects.

#### • **Calcitonin gene-related peptide (CGRP) receptor antagonists**

Olcegepant (BIBN40965BS) is administered intravenously and was effective and well tolerated in phase II trials, without vasoactive effects in cerebral circulation. It was never taken beyond phase II, because olcegepant has low oral bioavailability and it can be administered only by parenteral route, limiting thus its use in clinical practice [15].

Telcagepant (MK-0974) was administered orally in acute migraine treatment with positive results in phase III clinical trials, comparing the effects of 300 mg and 150 mg telcagepant with 5 mg zolmitriptan and *placebo*.

Telcagepant 300 mg was more effective than *placebo* in treating the migraine attack. Telcagepant 300 mg had a similar efficacy with 5 mg zolmitriptan, and both were more effective than 150 mg telcagepant.

Telcagepant blocks the dilatation of dural vessels and reduces the neurotransmission in CNS, without causing vasoconstriction, so it may be used in migraineurs with coronary disease.

In some patients, telcagepant caused elevation of liver transaminases. Due to this side effect, telcagepant cannot be used on a daily basis as a preventive migraine treatment.

Liver toxicity is not expected in intermittent use, so, telcagepant could still be an alternative to triptans in acute migraine treatment. Future studies are needed to confirm its safety [16].

#### • **Monoclonal antibodies (mAbs) targeting the CGRP**

Other way to diminish CGRP effects is the use of CGRP scavengers - substances that reduce the circulating levels of CGRP. Monoclonal antibodies (mAbs) targeting the CGRP have great specificity,

prolonged half-lives and reduced potential for hepatotoxicity and drug-drug interactions, avoiding the „gepants” (CGRP-Ras) problems. In these conditions, mAbs are suitable for long term use as preventive treatment of migraine [17, 18].

They are studies concerning mAbs as prophylactic treatment for both episodic migraine and chronic migraine. Anti-CGRP monoclonal antibodies (LY2951742, ALD403, and LBR101) and anti-CGRP-r monoclonal antibody (AMG334) could offer new opportunities to migraine patients [19].

Even the phase I and II clinical trials are promising, a long-term follow-up of these therapies is still needed [19].

#### ◆ **Glutamate receptor antagonists**

Glutamate is the most important excitatory neurotransmitter in the central nervous system and acts through:

- ionotropic glutamate receptors (iGluR) (ligand-gated channels) – of 3 subtypes – NMDA (N-methyl-D aspartate), AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoazolepropionic acid) and kainate, and
- G-protein coupled metabotropic receptors.

Genetic factors are important in migraine pathophysiology. A recent genome-wide associated study found a sequence variant on 8q22.1 in the inheritance of migraine, that is flanked between 2 genes involved in glutamate homeostasis [20]. These findings are important for better treatment guidance by pharmacogenetics.

Glutamate has an important role in trigeminovascular activation, central sensitization and cortical spreading depression. The glutamate neurons from the trigeminal ganglia express 5-HT<sub>1B/1D/1F</sub> receptors [21]. Experimentally, in cats, the blockade of AMPA receptor produced a dose-dependent inhibition of trigeminovascular evoked responses [22].

Tezampanel (LY-293558) is an AMPA and kainate receptor antagonist. It was studied in phase II trials with positive results in treating headache. Administered intravenously its effect was smaller than sumatriptan injections, but with fewer side effects [23, 24].

#### ◆ **“Capsaicin” receptor blockers**

“Capsaicin” receptor blockers are also termed transient receptor potential vanilloid (TRPV1) receptor antagonists. TRPV1 receptors are sensitive to capsaicin, heat and acidic conditions. They are located both in the central and peripheral trigeminal system. They may be involved in neurogenic inflammation and central sensitization, so they could be a target for new anti-migraine drugs [25].

A TRPV1 antagonist - (SB-705498) may be an effective suppressant and reversal agent of the central sensitization, due to sensory input which follows inflammation in the trigeminovascular

sensory distribution, but it may not be useful in blocking primary pain processes such as migraine headache [26]. So, this is not a suitable candidate for acute treatment of migraine attacks, but could be useful in “transformed” migraine.

Trials of CIVAMIDE - a TRPV1 antagonist - have negative results in acute migraine treatment [27].

#### ◆ **Nitric oxide (NO) synthesis inhibition**

NO is a gaseous molecule that regulates the arterial diameter in cerebral and extra-cerebral vessels and could be involved in migraine pathogenesis, NO can activate trigeminovascular fibres resulting the CGRP release [28].

Glyceryl trinitrate (NO donor) administered intravenously induces migraine-like headache in all individuals. NO is produced by degradation of L-arginine by NOS (nitric oxide synthase). NOS has 3 isoforms: endothelial (eNOS), neuronal (nNOS) and inducible (iNOS). GW274150 – is a selective iNOS inhibitor that failed to demonstrate efficacy in acute migraine in a recent study [29]. NXN-188 is a nNOS inhibitor and a 5-HT<sub>1B/1D</sub> receptor agonist with positive results in a phase II, multicentre, randomized controlled study, with mild to moderate adverse events [30].

Hydroxycobalamin, NO scavenger, administered intranasal reduced migraine frequency in an open study [31].

#### ◆ **Prostanoid receptor antagonists**

Prostaglandin E2 (PGE2) is a mediator for pain and inflammation, acting on several receptors: EP1 and EP3 responsible for smooth muscle contraction, and EP2 and EP4 responsible for smooth muscle relaxation. EP4 can be involved in prostaglandin-induced cerebral vasodilatation in acute migraine.

PGE2 levels are elevated in the jugular venous blood during migraine attacks [32]. So, prostaglandin E2 receptor blockers could play a role in migraine treatment. The blocker BGC-1531 can counteract PGE2-induced vasodilatation in cranial arteries, with no coronary effect *in vitro* [33].

#### ◆ **Anticonvulsants for migraine treatment**

Well known anticonvulsants drugs like valproate [34] and topiramate are approved for migraine prophylactic treatment [3]. There are many clinical and pathophysiological reasons that support anticonvulsants use in migraine treatment.

Migraine and epilepsy are characterised by episodes of neurological dysfunction, sometimes being difficult to differentiate migraine aura from simple partial seizures aura. Migraine and epilepsy could be comorbid. Migraine aura could trigger an epileptic seizure and, on the other hand, headache could be attributed to an epileptic seizure (post-ictal headache) [1].

Mutations leading to dysfunction of ion channels are present both in migraine and epilepsy, the two

conditions being considered as genetic neuronal channelopathies. Familial hemiplegic migraine (FHM) is a rare autosomal dominant disorder characterized by episodes of transient hemiparesis followed by headache, associated to several gene mutations:

- CACNA1A gene (FHM1), on chromosome 19 (coding for a calcium channel) [35];
- ATP1A2 gene mutation (FHM2), on chromosome 1 (coding for  $K^+ / Na^+$ -ATPase [36];
- SCN1A gene (FHM3), on chromosome 2 (coding for sodium channel) A novel locus for FHM (type 3) [37].

Modern neuroimaging techniques as PET (positron emission tomography) revealed brainstem activation during acute migraine, contralateral to hemicrania, and also the persistence of activation after the attack [38, 39].

Migraine is a primary disorder of the brain that may be caused by dysfunction of an ion channel in the aminergic brain-stem nuclei that normally modulates sensory inputs and exerts neural influences on cranial vessels. Migraine is a form of neurovascular headache in which neural events results in the dilatation of blood vessels, which, in turn, results in pain and further nerve activation [40]. Migraine aura is the human homologue of "cortical spreading depression" (CSD) found by Leao on rabbit cortex. Oligaemia is the reduction in regional cerebral blood flow, in response to depressed neuronal function. Oligaemia passes across the cortex from the occipital to frontal area, at a slow rate, without respecting the territory of single blood vessels [41]. The cortical spreading depression and the spreading oligoemia are preceded by a front of neuronal hyperactivity illustrated by abnormal epileptiform discharges on EEG (electroencephalography) [41]. The intense neuronal activity is followed by efflux of  $K^+$  from nerve cells; the glial cells (astrocytes) are involved in the clearance of brain  $K^+$ . The human cortex has the lowest ratio of glial to neuronal cells, suggesting a reduced threshold for CSD.

Sodium valproate and topiramate have proven efficacy in migraine preventive treatment, comparable to beta-blockers and flunarizine [3].

Sodium valproate (VPA) facilitates the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). It is effective in migraine prevention mainly when migraine occurs with comorbid epilepsy, anxiety disorders or manic-depressive illness or patients who have contraindications to beta-blockers (depression, Raynaud's disease, asthma, diabetes). The main side effect is hepatotoxicity; other effects are sedation, hair loss, tremor and changes in cognitive performances [3, 42]. Topiramate (TPM) is a sulfamate-substituted monosaccharide, derived from D-fructose, with multiple pharmacological actions: blockade of

sodium channels and high-voltage-activated calcium channels, attenuation of kainate-induced responses and enhancement of GABA-ergic neurotransmission. It also inhibits carbonic anhydrase activity.

It is effective in migraine prevention mainly in obese patients (anorexia and weight loss are frequent side effects) and also in refractory headaches. The main side effect is nephrolithiasis, besides other CNS side effects: poor concentration, paraesthesia, somnolence, cognitive slowing [3, 43-45]. Anticonvulsant drugs could be use also for reducing migraine aura. Lamotrigine (LTG) selectively blocks the slow inactivated state of sodium channels, thereby preventing the release of excitatory amino-acid neurotransmitters, particularly glutamate and aspartate. LTG is probably effective in reducing the frequency of migraine auras [46]. Rash can appear at the treatment initiation, so gradual introduction is needed.

Tonabersat is a neuronal-glia gap junction inhibitor. In clinical trials, it demonstrated the reduction of aura, but not the frequency of headache in patients with migraine with aura [47].

#### ◆ Botulin toxin for migraine treatment

Botulin toxin – used in several neurological diseases like dystonias, spasticity [48] proved to be efficient also in chronic migraine. In PREEMPT studies, Onabotulinumtoxin A 155 U or *placebo* was administered as 31 fixed-sites, fixed-dose injections across 7 specific head/neck muscle areas, the injection cycles were rejected after 14 weeks. There was a great decrease of the number of headache days between the 2 groups, favouring onabotulinumtoxin A group *versus placebo*.

Onabotulinumtoxin A blocks the release of pain neurotransmitters (substance P, calcitonin gene-related peptide CGRP) and glutamate - from the peripheral termination of primary afferents [50-52].

#### Conclusions

Although the triptans are highly effective in treating migraine attacks, vasoconstriction in cerebral and coronary territory limits their use.

New neural targets like: 5-HT<sub>1F</sub>, CGRP, glutamate, TRV1, mPE4, NOS [24] are recognised, maybe others will emerge in the future [35]. New molecules for migraine treatment [24], are on pipeline, hoping that in the future these will improve the quality life of migraine patients in the "post-triptan" era.

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