Novel strategies for the treatment of migraine attacks via the CGRP, serotonin, dopamine, PAC1 and NMDA receptors

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Abbreviation

5-HT: 5-hydroxytryptamine, Serotonin

$5\text{-}HT_{1F}$: 5-hydroxytryptamine 1F

AMPA: α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid

CGRP: calcitonin gene-related peptide

CGRP-RAs: calcitonin gene-related peptide receptor antagonists

CLR: calcitonin receptor-like receptor

CSD: cortical spreading depression

GPCR: G-protein-coupled receptor

iGluRs: ionotropic glutamate receptors

KYNA: kynurenic acid

LC: locus coeruleus

L-KYN: L-kynurenine

NMDA: N-methyl-D-aspartate

NRM: nucleus raphe magnus

NTG: nitroglycerin

PAC1: pituitary adenylate cyclase-activating polypeptide type 1

PACAP: pituitary adenylate cyclase-activating polypeptide

PAG: periaqueductal grey matter

RAMP1: receptor activity modifying protein 1

SpC5: spinal trigeminal nucleus

T_{max}: time to maximum concentration

TNC: trigeminal nucleus caudalis

TRIG: trigeminal ganglion

TS: trigeminovascular system

VIP: vasoactive intestinal peptide

Abstract

Introduction: Migraine is a common, paroxysmal, disabling primary headache with a high personal and socio-economic impact. It involves approximately 16% of the general population. During the years, a number of hypotheses have been put forward concerning the exact pathomechanism, but the final solution is still undiscovered.

Areas covered: Although the origin is enigmatic, parallel therapeutic efforts have been developed. Current attack therapy does not meet the expectations of the patients or the doctors. This article, based on a PubMed search, reviews the novel pharmacological possibilities that influence the peripheral and central sensitization involved in the disease.

Expert opinion: In order to overcome the therapeutic insufficiency, a CGRP receptor antagonist without the side-effect of liver transaminase elevation is required. Another therapeutic option is to develop a neurally acting anti-migraine agent, such as a serotonin-1F receptor agonist, with low adverse central nervous system events. Development of a potent dopamine receptor antagonist is necessary to diminish the premonitory symptoms of migraine. A further option is to decrease the headache intensity with a PAC1 receptor blocker which can cross the blood-brain barrier. Finally, synthetic kynurenine analogues are required to block the pain transmission in the activated trigeminal system.

Key words: 5-hydroxytryptamine 1F receptor agonist; calcitonin gene-related peptide receptor antagonists; dopamine receptor antagonists; migraine attack therapy; *N*-methyl-D-aspartate receptor inhibitors; pituitary adenylate cyclase-activating polypeptide type 1 receptor

1. Introduction

Migraine is a devastating neurovascular disorder with a high socio-economic and personal impact. It is characterized by episodic attacks of throbbing and pulsating headache associated with nausea, vomiting, photo- and phonophobia, cephalic and extracephalic allodynia and vertigo. It is a very common disorder, afflicting nearly 16% of the adult population . Despite the currently recommended guidelines concerning the treatment of an acute migraine attack, with analgesics, antiemetics, ergot alkaloids and triptans, many migraineurs fail to respond optimally. The majority of the treated patients do not attain a pain- free status within 2 h after taking the medication, or the headache recurs within 24 h . The aim of this review is to discuss promising pharmacological treatments of migraine attacks, focusing on calcitonin gene-related peptide (CGRP) receptor antagonists, 5-hydroxytryptamine 1F (5-HT_{1F}) receptor agonis, dopamine receptor antagonis, and possible pharmacons that act on the pituitary adenylate cyclase-activating polypeptide type 1 (PAC1) and N-methyl-D-aspartate (NMDA) receptors.

2. Calcitonin gene-related peptide receptor antagonists (CGRP-RAs)

CGRP is a 37-amino acid neuropeptide derived from the calcitonin gene, located on chromosome 11, that belongs in the calcitonin gene peptide superfamily . In humans, CGRP has two isoforms (α- and β- CGRP) which differ in the amino acids located at positions 3, 22 and 25 . It is a potent vasoactive neuropeptide that plays an important role in the pathomechanism of migraine headache, especially in the trigeminovascular system (TS). A classical study elegantly demonstrated an elevated concentration of CGRP in the cranial outflow in the jugular vein during a migraine attack . Numerous (up to 50%) CGRP-immunoreactive neurons are to be found in the trigeminal ganglion (TRIG) . The intravenous administration of CGRP proved to cause migraine-like attacks in migraine subjects , and in migraine attacks provoked by sublingual glyceryl trinitrate, increased CGRP concentrations were observed, which normalized after the cessation of the migraine . The anatomical structure of the TS contains the pseudounipolar neurons in the TRIG, the pial and dural vasculature and the second-order nociceptive neurons in the trigeminal nucleus caudalis (TNC) . The peripheral branch of the pseudounipolar neurons innervates the vessel wall of the pial and dural vasculature, and the central nerve ending synapse in the second-order neurons in the TNC . During activation of the TS, as in a migraine attack, CGRP is released from both the peripheral and the central arch of the trigeminal neurons, and causes peripheral and central sensitization . The peripheral sensitization explains the throbbing nature of the headache and the worsening of the headache pain due to intracranial hypersensitivity during physical activity . The consequences of central sensitization include cephalic cutaneous allodynia and extracranial tenderness (Figure 1).

The receptor for CGRP has been identified as a G-protein-coupled receptor (GPCR) of the family B - subtype . It consists of three proteins: the 7-transmembrane spanning protein of the calcitonin receptor-like receptor (CLR), which forms the ligand-binding site with the single-transmembrane spanning protein of receptor activity modifying protein 1 (RAMP1), which determines the specificity and species-selectivity of the receptor , and the CGRP-receptor component protein (RCP) couples the receptor to intracellular signal-transduction pathways via the CLR and to adenylyl cyclase .

The CGRP receptor antagonists were developed to block the CGRP-induced vasodilation in the meninges and the pain transmission in the TNC without causing vasoconstriction.

2.1. Olcegepant (BIBN4096BS)

BIBN4096BS, *[R-(R*,S*)]-N*-[2-[[5-amino-1-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]pentyl]amino]-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]- 4- (1,4- dihydro-2-oxo-3(2*H*)-quinazolinyl)- 1-piperidinecarboxamide, was the first selective small molecule (K_i=0.010 nM) non-peptide CGRP-RA. Doods et al. demonstrated its pharmacological profile in *in vitro* experiments on SK-N-MC (a human neuroblastoma cell line) cell membranes . The main characteristic of the CGRP receptor expressed in the SK-N-MC cell line was similar to that of the cloned human CGRP1 receptor . BIBN4096BS exhibited high affinity for the human CGRP receptor (150-fold higher than its antagonist CGRP(8-37)) and strongly inhibited neurogenic vasodilation . Because of its relatively high molecular weight (Mw=870) and low bioavailability, it can be administered only intravenously . The pharmacokinetic profile revealed a dose-proportional mean maximum concentration, resulting in a terminal half-life ($T_{1/2}$) of ~ 2.5 hours. The mean renal clearance was approximately 2 l/h . It proved efficacious in the treatment of acute migraine attacks, with a low adverse event profile . The only disadvantage was the need for intravenous administration, which impeded its wide-spread clinical use (Table 1).

2.2. Telcagepant (MK-0974)

For oral administration, a new CGRP-RA, telcagepant (MK-0974: *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)hexahydro-2-oxo-1-(2,2,2-trifluoroethyl)-1*H*-azepin-3-yl]-4-(2,3-dihydro-2-oxo-1*H*-imidazo[4,5-b]pyridin-1-yl)-1-piperidinecarboxamide), was synthetized . On human CGRP-Rs, this is a potent antagonist, with K_i=0.77 nM . Its bioavailability in dogs was 35%, and the clearance was 17 ml/min/kg, while in rats the bioavailability was 20% and the clearance was 9.4 l/min/kg . The time to maximum concentration (T_{max}) was 1.5 h and $T_{1/2}$ was ~ 6 h .

A Phase II proof-of-concept study indicated that telcagepant was effective versus placebo during the acute treatment of migraine and had a similar effect to that of triptan (zolmitriptan) .

Despite its strong clinical effect in terminating migraine headache, the high incidence of liver toxicity (elevation of liver transaminases) during its long-term and frequent use prevented its wide-clinical utilization.

3. 5-Hydroxytryptamine 1F (5-HT_{1F}) receptor agonist

Serotonin (5-hydroxytryptamine, 5-HT) was first isolated from serum in the late '40s . Its role in migraine has been substantiated since the 1960s.

In 1961, Sicuteri et al. demonstrated the enhanced urinary level of 5-hydroxyindoleacetic acid (5-HIAA) during migraine attacks , and decreased plasma 5-HT level was also demonstrated during headache. The intravenous administration of 5-HT effectively alleviated migraine headaches, though with a wide range of side-effects.

The 5-HT receptors have been classified into seven major classes (5-HT1 to 5-HT7). Only the 5-HT1B, 1D, 1F and 2B receptor subtypes are involved in pain transmission. The discovery of triptans (selective 5-HT1B/1D receptor agonists) more than 20 years ago furnished very potent acute anti-migraine agents with selective pharmacology and consistent pharmacokinetics . The 5-HT1B receptor is located on the vascular smooth muscle, while 5-HT1D is expressed in the neuronal element of the TRIG . The main mechanism is based on cranial vasoconstriction, peripheral neuronal inhibition and blocking of the firing of nociceptive second-order neurons in the TNC. In consequence of 5-HT1B receptor agonism, they have the risk of causing coronary vasoconstriction and chest discomfort , which limit their use in daily practice.

To avoid the 5-HT1B receptor-mediated direct vasoconstrictor effect, 5-HT1F receptor agonists have been synthetized, as the 5-HT1F receptor does not affect the diameter or contractility of the blood vessels . The 5-HT1F receptor is located on the glutamatergic neurons within the TRIG . It has also been identified in the guinea pig hippocampus, cortex, claustrum and spinal trigeminal nucleus (SpC5) , and in the porcine cortex, TRIG and several blood vessels .

3.1. Lasmiditan (COL-144, LY573144)

Lasmiditan (2,4,6-trifluoro-*N*-[6-[(1-methylpiperidin-4-yl)carbonyl]pyridin-2yl]benzamide) is a highly selective 5-HT1F receptor agonist available from Eli Lilly. It does not contain the indole core, which defines the triptans and the first-generation 5-HT1F receptor agonist LY334370. An *in vitro* binding study showed its excellent selectivity (470-fold) for 5-HT1F receptors (K_i=2.21 nM) as compared with K_i values of 1043 and 1357 nM for 5-HT1B and 5-HT1D, and its functional activity *in vitro* was proved by Nelson et al. . The lack of a contractive effect of lasmiditan on rabbit saphenous vein rings was observed up to a concentration of 100 μM. Lasmiditan blocked trigeminal stimulation-induced dural plasma protein extravasation with an ID_{50} of 2 x 10^{-4} μg/kg, and decreased the number of c-fos- positive cells in the SpC5 at a dose of 3 mg/kg 1 h after oral administration . Thus, in view of its new site of action, it is a neurally acting anti-migraine agent.

The oral bioavailability of lasmiditan is 40%, and its T_{max} is 2 h (CoLucid Pharmaceuticals) . During a randomized proof-of-concept and dose-finding study, 130 subjects were treated with lasmiditan intravenously . The dose range was 2.5 mg to 45 mg. The results revealed a linear association between the response rates and dose levels. The effective intravenous dose was 20 mg or more . In a Phase II randomized, placebo-controlled, parallel-group, dose-ranging study, the efficacy of orally administered lasmiditan in a dose of 100 mg, or 400 mg (64-65%) was better than that of placebo (26%). The placebo-subtracted adverse events rate was 50% (95% CI: 37-63%) for 100 mg oral lasmiditan, and 66% (95% CI: 50-75%) for 400 mg . Even though this selective 5-HT1F receptor agonist has a high incidence of moderate or severe adverse central nervous system-related events, such as dizziness, fatigue, vertigo and paraesthesia, it is an alternative means of treatment for migraineurs who have contraindications for vasoconstrictor agents, such as triptans .

4. Dopamine receptor antagonists

With regard to the occurrence of nausea, vomiting and blood pressure changes during migraine attacks, Sicuteri proposed possible dopaminergic activation in migraine . Although this theory has not been substantiated during the years, some recent results suggested that dopamine may be involved in the pathogenesis of migraine.

Dopamine is one of the three naturally-occurring catecholamines. Dopamine receptors belong in the group of G protein-coupled receptors. On the basis of their structural and pharmacological properties, the dopamine receptors are divided into the D1- and D2-like family receptors. The D1-like family receptors (D1 and D5) activate adenylyl cyclase and consequently increase the intracellular concentration of cAMP, while activation of the D2-like family receptors (D2, D3 and D4) inhibits the formation of cAMP .

The findings that administration of the dopamine agonist apomorphin enhanced nausea, vomiting and yawning, and that the platelet levels of dopamine were increased in migraine supported the theory of hypersensitivity to dopamine in migraineurs .

D1 and D2 dopamine receptors can be found in the rat TRIG, mesencephalic trigeminal nucleus and trigeminocervical complex , which links dopamine to the TS.

Molecular genetic studies have revealed an increase in the polymorphism of the DRD2 encoding Nocardia corallina-1 (Nco1) gene and DRD4 polymorphism in migraine without aura. A decreased allelic distribution of dopamine-β-hydroxylase polymorphism was also observed, accompanied by an increased dopamine level in migraineurs .

4.1. Prochlorperazine

The intravenous administration (5 to 10 mg) of prochlorperazine led to a response rate of 88%, as compared with 45% for placebo. The headache relief duration was 30 min . Oral doses of 5 or 10 mg, and suppositories of 25 mg were useful. A long QTc interval is a contraindication. The most common adverse events are akathisia, sedation and tachycardia .

4.2. Chlorpromazine

Chlorpromazine relieved pain, nausea, phono- and photophobia in 1 h (95%) in an intravenous dose of 0.1 mg/kg . The main side-effects were postural hypotension, drowsiness and akathizia .

4.3. Metoclopramide

Metoclopramide has an indication for the treatment of nausea and vomiting, and it may promote the gastrointestinal absorption of other medications, such as aspirin and acetaminophen . The standard dose is 5 to 20 mg for both oral and intravenous administration .

4.4. Domperidone

Domperidone is a peripheral DRD2 antagonist, because of its poor blood-brain barrier penetration. In a 20 to 30 mg dose, combined administration with 1000 mg paracetamol decreased the duration of migraine attacks by 30% . In a dose-finding study, domperidone prevented 30% of attacks in a dose of 20 mg, 58% in 30 mg and 63% in 40 mg . No side- effects were published.

4.5. Haloperidol

Significant migraine pain relief was observed in 80% of migraineurs after intravenously administered haloperidol (5 mg) . The main adverse events were sedation and akathisia .

4.6. Droperidol

A randomized, double-blind, placebo-controlled, dose-ranging, multicentre study found that the 2 h headache response rate was significant following the intramuscular administration of droperidol in a dose of 2.75 mg. Anxiety, akathisia and somnolence were the main adverse events . Droperidol is also contraindicated in the event of a long QTc interval .

This D2-dopamine receptor antagonist decreases only the premonitory symptoms of migraine, but also alleviates the headache in combination treatments by ameliorating the gastric absorption.

5. Pituitary adenylate cyclase- activating polypeptide type 1 (PAC1) receptor

Pituitary adenylate cyclase- activating polypeptide (PACAP), the newest member of the vasoactive intestinal peptide (VIP)/secretin/glucagon neuropeptide superfamily, was first isolated from the ovine hypothalamus . In humans, PACAP is encoded by the ADCYAP1 gene (propeptide of 175 amino acids) and occurs in two biologically active forms, the C-terminally truncated PACAP-27 and PACAP-38 (27 or 38 amino acids), with the predominant occurrence of PACAP-38 . PACAP-38 does not pass the blood- brain barrier as it is a large molecule . The plasma elimination half-life of PACAP-38 is less than 5 min .

Immunohistochemical studies have demonstrated the expression of PACAP in the parasympathetic and sensory ganglia , the human TNC and the C1 and C2 levels of the cervical spinal cord . PACAP displays a large variety of biological effects, including neuroprotection, stimulation of cell proliferation and differentiation, and an anti- apoptotic effect .

In recent years, numerous data have been published on the role of PACAP in pain transmission and the pathomechanism of primary headaches .

Preclinical experimental studies suggested the crucial role of PACAP-38 in TS activation . Stimulation of the superior sagittal sinus, which is densely innervated by the peripheral branch of the perykarya of the

TRIG, resulted in an increased level of PACAP in the cranial outflow . One of the main concomitant features of a migraine attack is photophobia. A reduced level of light-aversive behavior has been demonstrated in PACAP gene-deleted mice after nitroglycerin (NTG) administration, and PACAP-38 elicited light-aversion in wild-type mice . During electrical TRIG stimulation in rats, an increased plasma level and TNC concentration of PACAP-38 were observed .

Schytz et al. demonstrated that the intravenous administration of PACAP-38 resulted in headache in healthy subjects, and in migraine-like headache in migraineurs without aura 4-5 h after the infusion, increasing the diameter of the superficial temporal arteries and decreasing the mean blood flow velocity of the middle meningeal arteries . PACAP-38 infusion caused the pronounced dilatation of the extracranial, but not the intracranial arteries . It was interesting that another member of this neuropeptide superfamily, VIP, did not induce migraine headache on intravenous administration and the VIP-induced dilation was normalized in a shorter period relative to PACAP-38 induced vasodilation . In an *in vivo* human study, the plasma concentration of PACAP-38 proved to be significantly lower in the interictal period in migraineurs as compared with healthy individuals, and increased significantly during the ictal period .

These findings open the way for further research to identify specific cause-related therapy.

The effects of PACAP are mediated through the class B family of 7-transmembrane GPCRs, i.e. VPAC1, VPAC2 and PAC1 . PACAP is 1000-fold more potent than VIP at the PAC1 receptor , while VIP and PACAP bind to the VPAC1 and VPAC2 receptors with equal affinity . As a result of the activation of PACAP receptors, increases in the levels of cAMP, phospholipase C and intracellular calcium were observed . In view of the different PACAP and VIP receptor kinetics and the human observations that PACAP did, but VIP did not induce a migraine attack, the PAC1 receptor may be a future candidate as a therapeutic target. Until now only one PAC1 receptor agonist (maxadilan) is available, which was isolated from salivary glands of the sand fly *Lutzomyia longipalpis* . It is a 61-amino acid peptide. For its activity the integrity of the ring between 14 and 51 is necessary. On the other hand the deletion of the amino acids between 25 and 41 generated a specific PAC1 receptor antagonist, termed M65 . A recent study proved that maxadilan had no effect on CGRP release and M65 did not block the PACAP-38-induced CGRP release in the TS . An additional task for drug development procedures is to create a PAC1 receptor blocker which can cross the blood-brain barrier to reach the possible migraine related structures.

6. N-Methyl-D-aspartate (NMDA) receptors

Glutamate is the main excitatory amino acid in the mammalian central nervous system. Both experimental and human studies have indicated the role of glutamate in the pathogenesis of migraine . Animal studies revealed the presence of glutamatergic neurons in the TRIG , and dural and trigeminal nerve stimulation increased the level of glutamate in the TNC . In human studies, an elevated level of glutamate was observed in the cerebrospinal fluid , the plasma and the saliva in migraine patients.

The glutamate-induced excitability is mediated via ionotropic (iGluRs) and metabotropic glutamate receptors. The iGluRs are glutamate-gated ion channels that mediate fast synaptic transmission. They are subdivided into three subtypes: NMDA, α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) and kainate . NMDA receptors form tetrameric assemblies of seven subunits, NR1, NR2A-D and NR3A-B. For the activation of NMDA receptors, the binding of glutamate and a co-agonist glycine or D-serine is needed . The NMDA receptor protein complex contains a binding site within the channel pore for Mg^{2+}; it is permeable to Na^{+}, K^{+} and Ca^{2+} and sites of action for polyamines, zinc and protons are also found in the NR2 subunit . NMDA receptors are expressed in the superficial laminae of the TNC in rat , in the TRIG and in the thalamus , and they are also involved in central sensitization .

Cortical spreading depression (CSD) is a propagating transient negative direct potential shift, which occurs in migraine with aura . Elevation of the extracellular concentration of K^{+} is a potent trigger of CSD . The inhibition of this process by NMDA receptor antagonists emphasizes the action of glutamate in the initiation of CSD .

The possible effects of NMDA receptor antagonists have been examined in animal models and clinical trials.

6.1. MK-801

MK-801, a non-competitive NMDA receptor channel blocker, has been found to reduce Fos-like immunoreactivity and decrease the increased local blood flow in the cat trigeminocervical complex after stimulation of the superior sagittal sinus , to inhibit CSD , and to decrease the neurogenic dural vasodilation , but to increase the neuronal activity in the descending anti-nociceptive system (the ventrolateral periaqueductal grey matter (PAG), nucleus raphe magnus (NRM), dorsal raphe nucleus and Edinger-Westphal nucleus) . During spontaneous migraine attacks, an increased blood flow of specific brainstem nuclei, such as the NRM, PAG locus coeruleus (LC) ("migraine generators") was observed by high-resolution positron emission tomography . Human immunohistochemical studies revealed CGRP, PACAP immunoreactive fibres and neurons in the LC, and substance P afferentation in the PAG and RNM . These observations suggested that these specific nuclei influence the activation of TNC. Human Phase I studies are required.

6.2. Memantin

Memantin is another non-competitive NMDA receptor blocker, with an effect of CSD prevention . In a clinical study, memantin in a dose of 10 to 20 mg was effective as preventive treatment of refractory migraine, as it significantly decreased the monthly headache frequency and the mean disability score . On the other hand, 37.5% of the patients reported side-effects, such as somnolence, asthenia, anxiety, depression and an increase in weight .

6.3. L-701,324

L-701,324 is an NMDA glycine-site antagonist. On systemic administration it inhibited CSD in rats .

6.4. Ketamine

Ketamine, a non-competitive NMDA receptor antagonist, reduced neurogenic dural vasodilation in an experimental model . In a very small human study (n=11) designed to examine the effect of intranasally administered (25 mg) ketamine in migraineurs with familial hemiplegic migraine, 5 patients manifested beneficial effects. It reduced the severity and duration of the aura symptoms .

6.5. Kynurenines

Recent preclinical experimental data suggested a connection between the kynurenines and the pathomechanism of migraine . The tryptophan metabolism has two major pathways: the well-known 5-HT pathway, and the lesser-known L-kynurenine (L-KYN) pathway, which also has an important impact, as kynurenic acid (KYNA) is one of the very few endogenous NMDA receptor antagonists . Its 40% is produced locally in the central nervous system, while the remaining 60% is taken up from the blood . KYNA (4-hydroxyquinoline-2-carboxylic acid) is produced from L-KYN by neurons and astrocytes . At 7.9 μM, KYNA effectively inhibited the NMDA receptors via attachment to the glycine-binding site . It is to be noted that KYNA has a concentration-dependent neuromodulatory effect, like a Janus-face compound. In a nanomolar concentration it facilitates, while in a micromolar concentration it inhibits the NMDA and AMPA receptors . In an animal migraine model chemically induced by NTG, c-fos and calmodulin-dependent protein kinase II alpha activation occurred in the second-order nociceptive neurons, an effect which was inhibited by the KYNA precursor L-KYN . Concerning the blood-brain barrier penetration only the L-tryptophan, L-KYN and 3-hydroxy-l-kynurenine can be transported, while KYNA can poorly penetrate. The halogenated derivative 4-chlorokynurenine can be transported through the blood-brain barrier as L-KYN, and therefore causing the release of 7-chlorokynurenic acid from astrocytes .

As an endogenous NMDA receptor antagonist, KYNA influences pain transmission via second-order neurons in the TNC and can modulate pain-control through the brainstem "migraine generators". Good blood-brain barrier-penetrating synthetic KYNA analogues are needed for a human Phase I study.

7. Conclusions

Migraine afflicts 16% of the general population world-wide, but the exact pathomechanism and cause-related attack therapy are still unsolved. The leading hypothesis postulates that CGRP is a migraine-related neuropeptide. The functional CGRP receptor has been described and its antagonists have been developed. They have beneficial effects on migraine headache, without side-effects of coronary constriction such as those of triptans. The disadvantage of these pharmacons is the related liver toxicity, which prevents their wide-spread clinical use. The 5-HT-1F receptor agonist lasmiditan is a neurally acting anti-migraine agent which proved effective in clinical studies, but the severe adverse central nervous system-related events limit its usage. Another possible target is the D2-dopamine receptor; its antagonists in a single therapy influenced only the premonitory symptoms of migraine, and not headache pain. Nowadays the preclinical data indicate that the PAC1 receptor is a target for new therapeutic options for migraine. Recent experimental studies demonstrated that the excitatory receptors takes part in the activation of the TS, and its antagonists are promising future therapeutic candidates.

8. Expert Opinion

Migraine is a very devastating neurovascular disorder accompanied by severe headache pain and concomitant clinical conditions such as photo- and phonophobia, nausea, vomiting, vertigo, and cephalic and extracephalic allodynia. Both patients and neurologists seek the attainment of rapid and complete relief from pain and the associated symptoms with safety, good tolerability and a low side-effect profile, with simple administration and low price. Medication with a good pharmacokinetic profile can fulfil these expectations.

During the past 15 years, the gold standard of acute migraine therapy has been based on the use of triptans, highly selective 5-HT1B/1D receptor agonists that cause vasoconstriction via the 5-HT1B receptors and inhibit neuropeptide (e. g. CGRP) release from the trigeminal nerve endings. They can diminish headache pain with high efficacy. They are available for different administration routes as tablets, orally disintegrating tablets, intranasal sprays, rectal suppositories and subcutaneous injections, which are favoured by the patients. The problem is that they do not cover the overall population of migraineurs and the related coronary vasoconstriction. To avoid vasoconstriction, and to diminish CGRP-induced TS activation, CGRP-RAs ("gepants") have been developed. The first was olcegepant, which proved very efficacious in alleviating the pain, but its disadvantage was the intravenous administration route, which prevented its wide-spread clinical use. A new type of CGRP-RAs, telcagepant, was synthetized for oral administration. The Phase II proof-of-concept study demonstrated its effectivity versus placebo and the comparison with triptan (zolmitriptan) revealed a similar effect. The problem with this drug was the liver toxicity (elevated liver transaminase) on long-term and frequent use. The task for future pharmaceutical research is to develop a CGRP-RA without liver toxicity.

Another way to avoid the 5-HT1B receptor-mediated direct vasoconstrictor effect is the synthesis of 5-HT1F receptor agonists, as neurally acting anti-migraine agents. The recently developed highly selective 5-HT1F receptor agonist lasmiditan was superior to placebo in diminishing the headache, but its severe central nervous system-related side-effects, such as dizziness, fatigue, vertigo and paraesthesia, limit its use.

Migraineurs are hypersensitive to dopamine and in migraineurs without aura the polymorphism of DRD2 encoding gene has been observed. Well-known DRD2 antagonists tested in migraine attacks, mitigated only the premonitory symptoms. It should be highlighted that these drugs combined with aspirin, acetaminophen or paracetamol alleviated the headache by ameloriating the gastric absorption.

Numerous data have been published on the role of PACAP in pain transmission and the pathomechanism of primary headaches. In contrast with VIP, which is also a member of the secretin/glucagon neuropeptide superfamily and a well-known vasodilator, only PACAP-38 induced migraine headache after intravenous administration. This feature of PACAP-38 was similar to that of intravenously administered alpha-CGRP. Moreover, during a spontaneous migraine attack the plasma level of PACAP-38 is significantly elevated as compared with the headache-free period, as for CGRP during the attack in the cranial outflow. Immunohistochemical studies have revealed that CGRP and PACAP-38 are located in the trigeminal pseudounipolar neurons. It is possible that they have a common role in activating the TS. PACAP and VIP have common receptors, VPAC1 and VPAC2, while the PAC1 receptor is specific for PACAP. Analogously to the CGRP-RAs, PAC1 receptor antagonists should be developed, with a capability of blood-brain barrier penetration.

One of the receptors of the main excitatory amino acid, glutamate, is the NMDA receptor. Glutamate has a crucial role in TS activation. Synthetic NMDA receptor channel blockers have been tested in part in human studies, but need to reach the Phase I study level. The recent preclinical experimental data suggested a connection between the kynurenines and TS activation. KYNA is one of the very few endogenous NMDA receptor antagonists. The drawback of this substance is its very poor blood-brain barrier penetration. In order to organize a proof-of-concept human study, the development of good blood-brain barrier- penetrating synthetic analogues is required.

Each of the above-mentioned molecules have beneficial characteristics, but more development and Phase studies are needed for their final evaluation.

Highlights

- The pathomechanism of migraine and the therapy of migraine attacks are still unsolved.
- Calcitonin gene-related peptide receptor antagonists are effective without the side-effect of coronary construction, but the related liver toxicity prevents their wide-spread clinical use.
- The 5-hydroxytryptamine 1F receptor agonist is effective as a neurally acting anti-migraine agent, but the severe adverse central nervous system-related events limit its clinical use.
- The D2-dopamine receptor antagonists alone, merely influence the premonitory symptoms of migraine, and not the pain.
- The pituitary adenylate cyclase-activating polypeptide type 1 receptor blocker is a future candidate for migraine therapy, but its blood-brain barrier penetration is poor.
- *N*-Methyl-D-aspartate receptor antagonists are promising experimentally, but Phase I studies are necessary.

Declaration of interest

The authors declare that they have no conflict of interest and have received no payment in preparation of their manuscript.

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- **The authors described the effect of L-kynurenine and a novel kynurenic acid derivative on pain transmission in the activated trigeminovascular system.**

Table

Table 1 Distribution of receptors in migraine related structures and receptor-binding compounds for migraine treatment

Receptor	**Migraine related structures**	**Receptor agonist**	**Receptor antagonist**
CGRP	Trigeminal ganglion Trigeminal nucleus caudalis Sphenopalatine ganglion Cerebral dura mater Cerebellar cortex		Olcegepant Telcagepant
5-HT1F	Trigeminal ganglion Trigeminal nucleus caudalis Cerebral cortex	Lasmiditan	
D2-Dopamine	Trigeminal ganglion Trigeminal nucleus caudalis		Prochlorperazine Chlorpromazine Metoclopramide Domperidone Haloperidol Droperidol
PAC1	Trigeminal ganglion Trigeminal nucleus caudalis Sphenopalatine ganglion Thalamus Hypothalamus Cerebellum	Maxadilan	M65
NMDA	Trigeminal ganglion Trigeminal nucleus caudalis Thalamus		MK-801 Memantin L-701,324 Ketamine Kynurenate derivative

Figure legend

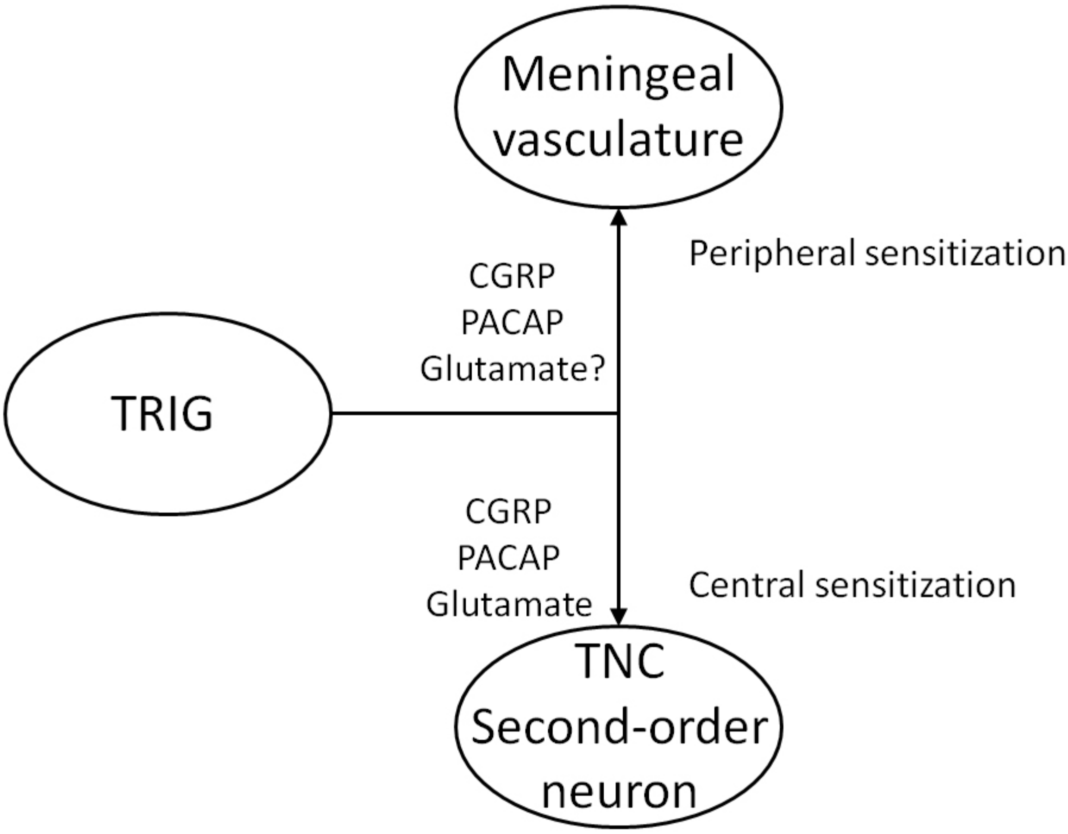

Figure 1 Scheme of the trigeminovascular system (TS).

The peripheral branch of the pseudounipolar neurons in the trigeminal ganglion (TRIG) innervates the vessel wall of the pial and dural vasculature, and the central nerve ending synapse in the second-order neurons in the trigeminal nucleus caudalis (TNC). During activation of the TS, as in a migraine attack, calcitonin gene-related peptide (CGRP), glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) are released from the peripheral and the central arch of the trigeminal neurons, which causes peripheral and central sensitization.