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

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Introduction: Migraine is a common, paroxysmal, and disabling headache with a high personal and socioeconomic impact. It involves ~ 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 calcitonin gene-related peptide receptor antagonist without the side-effect of liver transaminase elevation is required. Another therapeutic option is to develop a neurally acting antimigraine 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 pituitary adenylate cyclase-activating polypeptide type 1 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.

Keywords: 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 socioeconomic 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 [1]. 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 even within 2 h after taking the medication, or the headache recurs within 24 h [2]. In patients who have frequent attacks and do not respond to the aforementioned medications, medication-overuse headache can occur. In an effort to treat such intractability, the use of central and peripheral neurostimulation techniques was initiated. In the acute treatment of migraine with or without aura, single-pulse transcranial magnetic

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Article 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 constriction, but the related liver toxicity prevents their wide spread clinical use.
- The 5-hydroxytryptamine 1F receptor agonist is effective as a neurally acting antimigraine agent, but the severe adverse central nervous system-related events limit its clinical use.
- The D2-dopamine receptor antagonists 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.

This box summarizes key points contained in the article.

stimulation, may be applied; while in the treatment of chronic migraine, transcranial direct current stimulation can be used as a type of central modulation. In the peripheral modulation of chronic migraine and episodic migraine, sphenopalatine ganglion stimulation and supraorbital nerve stimulation, respectively, are available [3]. It should be stressed that neurostimulation in migraine is currently in an immature status and large controlled studies, are needed.

The aim of this review is to discuss promising pharmacological treatments of migraine attacks, focusing on calcitonin gene-related peptide (CGRP) receptor antagonists, a 5-hydroxytryptamine 1F (5-HT$_{1F}$) receptor agonist, a dopamine receptor antagonist, and possible pharmacons that act on the pituitary adenylate cyclase-activating polypeptide type 1 (PAC1) and NMDA receptors.

2. Calcitonin gene-related peptide receptor antagonists

CGRP is a 37-amino acid neuropeptide derived from the calcitonin gene, located on chromosome 11, that belongs in the calcitonin gene peptide superfamily [4,5]. In humans, CGRP has two isoforms (α- and β-CGRP), which differ in the amino acids located at positions 3, 22, and 25 [6]. 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 [7]. Numerous (up to 50%) CGRP-immunoreactive neurons are to be found in the trigeminal ganglion (TRIG) [8]. The intravenous administration of human α-CGRP (2 μg/min) proved to cause migraine-like attacks in migraine subjects. An immediate

headache was observed in the first 60 min after the start of the infusion, and a delayed headache in the subsequent 11 h. The immediate headache did not, whereas the delayed headache did meet the International Headache Society criteria for migraine without aura [9]. In migraine attacks provoked by sublingual glyceryl trinitrate, increased CGRP concentrations were observed, which normalized after the cessation of the migraine [10]. 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) [11]. 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 [12-14]. 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 [12,15,16]. The peripheral sensitization explains the throbbing nature of the headache and the worsening of the headache pain due to intracranial hypersensitivity during physical activity [17]. The consequences of central sensitization include cephalic cutaneous allodynia and extracranial tenderness (**Figure 1**) [17].

The receptor for CGRP has been identified as a G-protein-coupled receptor (GPCR) of the family B-subtype [18]. 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, which determines the specificity and species-selectivity of the receptor [19,20], and the CGRP-receptor component protein (RCP) couples the receptor to intracellular signal-transduction pathways via the CLR and to adenylyl cyclase [21].

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) nonpeptide calcitonin gene-related peptide receptor antagonist (CGRP-RA). Doods *et al.* demonstrated its pharmacological profile in *in vitro* experiments on SK-N-MC (a human neuroblastoma cell line) cell membranes [22]. 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 [23]. BIBN4096BS exhibited high affinity for the human CGRP receptor (150-fold higher than its antagonist CGRP[8 – 37]) and strongly inhibited neurogenic vasodilation [22]. Because of its relatively high molecular weight (Mw = 870) and low bioavailability, it can be administered only intravenously [22]. The pharmacokinetic profile revealed a dose-proportional mean maximum concentration, resulting
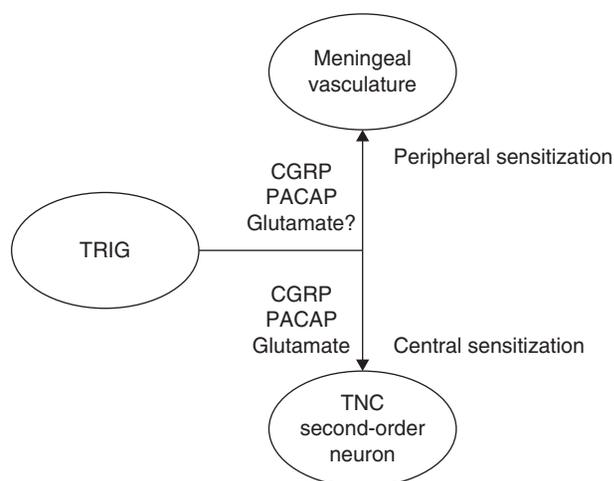
Figure 1. Scheme of the trigeminovascular system. The peripheral branch of the pseudounipolar neurons in the TRIG innervates the vessel wall of the pial and dural vasculature, and the central nerve ending synapse in the second-order neurons in the TNC. During activation of the TS, as in a migraine attack, CGRP, glutamate and PACAP are released from the peripheral and the central arch of the trigeminal neurons, which causes peripheral and central sensitization.

CGRP: Calcitonin gene-related peptide; PACAP: Pituitary adenylate cyclase-activating polypeptide; TNC: Trigeminal nucleus caudalis; TRIG: Trigeminal ganglion; TS: Trigeminovascular system.

in a terminal half-life ($T_{1/2}$) of ~ 2.5 h. The mean renal clearance was ~ 2 l/h [24]. A multicentre, double-blind, randomized (126 patients with migraine) study revealed that an intravenously administered 2.5 mg dose of olcegepant gave a high response rate (66%). From the aspects of the pain-free rate at 2 h, the 24-h sustained pain relief, and the rate of recurrence of the headache, it was statistically superior to placebo, and it led to improvements in nausea, photophobia, phonophobia, and functional capacity. The common side-effect was paraesthesia (7%), while nausea, dry mouth, and abnormal vision occurred in only 2% of the cases [25]. 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 synthesized [26]. On human CGRP-Rs, this is a potent antagonist, with K_i = 0.77 nM [27]. 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 [26]. The T_{max} was 1.5 h and $T_{1/2}$ was ~ 6 h [28].

In a randomized (1380 migraine patients) – parallel-treatment, placebo-controlled, double-blind – trial, telcagepant in

150 mg (n = 333) and 300 mg (n = 354) doses was compared with zolmitriptan (5 mg, n = 345) or placebo (n = 348). Telcagepant 300 mg was superior to placebo for pain freedom (27%), pain relief (55%), and the absence of phonophobia (58%), photophobia (51%), and nausea (65%). Telcagepant 300 mg and zolmitriptan 5 mg had the same effectiveness. Both were superior to telcagepant 150 mg. Telcagepant at a dose of 150 mg proved better than placebo. The most frequent side-effects during the use of telcagepant were dry mouth, somnolence and dizziness [29]. Another randomized, controlled trial studied telcagepant (140 and 280 mg) over four migraine attacks. Both were more effective than placebo (2 h pain freedom, 2 h pain relief, 2 – 24 h sustained pain freedom, and 2 h absence of migraine-associated symptoms, such as phonophobia, photophobia, and nausea). The frequent adverse events were somnolence and vomiting [30].

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.

2.3 Newly synthesized CGRP-RAs

Of the newly synthesized CGRP-RAs (MK-3207, MK-1602, BMS-694153, BI 44370 TA, BMS-927711), mention should be made of the highly potent (K_i = 0.027 nM), selective and competitive BMS-927711. A randomized, double-blind, multicentre, placebo-controlled, dose-ranging study was designed to determine the effective and tolerable dose of BMS-927711 for the acute treatment of migraine. In doses of 75 mg, (31.4%), 150 mg (32.9%), and 300 mg, 31.4, 32.9, and 29.7%, respectively, of the patients reported freedom from pain at 2 h postdose as compared with placebo (15.3%) and the tolerability profile was excellent [31-33].

3. 5-Hydroxytryptamine 1F (5-HT$_{1F}$) receptor agonist

Serotonin (5-hydroxytryptamine, 5-HT) was first isolated from serum in the late 1940s [34]. Its role in migraine has been substantiated since the 1960s. In 1961, Sicuteri *et al.* demonstrated a enhanced urinary level of 5-hydroxyindoleacetic acid (5-HIAA) during migraine attacks, and a decreased plasma 5-HT level during headache [35]. 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-HT$_{1B, 1D, 1F}$, and 2B receptor subtypes are involved in pain transmission. The discovery of triptans (selective 5-HT$_{1B/1D}$ receptor agonists) > 20 years ago furnished very potent acute antimigraine agents with selective pharmacology and consistent pharmacokinetics [36]. They have been developed for different administration routes as tablets, orally disintegrating tablets, intranasal sprays, rectal suppositories, and subcutaneous injections, which are favored by the patients. The 5-HT$_{1B}$ receptor is

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

Receptor	Migraine related structures	Ref.	Receptor agonist	Receptor antagonist	Ref.
CGRP	Trigeminal ganglion Trigeminal nucleus caudalis Sphenopalatine ganglion Cerebral dura mater Cerebellar cortex	[116]		Olcegepant Telcagepant	[22,27]
5-HT$_{1F}$	Trigeminal ganglion Trigeminal nucleus caudalis Cerebral cortex Cerebellum (granule cell layer)	[40-42,117]	Lasmiditan		[43]
D2-Dopamine	Trigeminal ganglion Trigeminal nucleus caudalis	[50,51]		Prochlorperazine Chlorpromazine Metoclopramide Domperidone Haloperidol Droperidol	[56]
PAC1	Trigeminal ganglion Trigeminal nucleus caudalis Sphenopalatine ganglion Thalamus Hypothalamus Cerebellum	[8,12,69,70]	Maxadilan	M65	[77]
NMDA	Trigeminal ganglion Trigeminal nucleus caudalis Thalamus	[86-88]		MK-801 Memantin L-701,324 Ketamine Kynurenate derivative	[92,93,95,100,102]

CGRP: Calcitonin gene-related peptide; PAC1: Pituitary adenylate cyclase-activating polypeptide type 1.

located on the vascular smooth muscle, while 5-HT$_{1D}$ is expressed in the neuronal element of the TRIG [37]. 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-HT$_{1B}$ receptor agonism, they have the risk of causing coronary vasoconstriction and chest discomfort [38], which limits their use in daily practice.

To avoid the 5-HT$_{1B}$ receptor-mediated direct vasoconstrictor effect, 5-HT$_{1F}$ receptor agonists have been synthetized, as the 5-HT$_{1F}$ receptor does not affect the diameter or contractility of the blood vessels [39]. The 5-HT$_{1F}$ receptor is located on the glutamatergic neurons within the TRIG [40]. It has also been identified in the guinea pig hippocampus, cortex, claustrum, and spinal trigeminal nucleus (SpC5) [41], and in the porcine cortex, TRIG, and several blood vessels [42].

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-HT$_{1F}$ receptor agonist available from Eli Lilly. It does not contain the indole core, which defines the triptans and the first-generation 5-HT$_{1F}$ receptor agonist LY334370. An *in vitro* binding study showed its excellent selectivity (470-fold) for

5-HT$_{1F}$ receptors (K_i = 2.21 nM) as compared with K_i values of 1043 and 1357 nM for 5-HT$_{1B}$ and 5-HT$_{1D}$, and its functional activity *in vitro* was proved by Nelson *et al.* [43]. 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 2×10^{-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 [43]. Thus, in view of its new site of action, it is a neurally acting antimigraine agent.

The oral bioavailability of lasmiditan is 40%, and its T$_{max}$ is 2 h (CoLucid Pharmaceuticals) [44]. During a randomized proof-of-concept and dose-finding study, 130 subjects were treated with lasmiditan intravenously [45]. The dose range was 2.5 – 45 mg. The results revealed a linear association between the response rates and dose levels. The effective intravenous dose was 20 mg or more [45]. In a Phase II randomized, placebo-controlled, parallel-group, dose-ranging study, the efficacy of orally administered lasmiditan in a dose of 100 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 [46]. The cardiovascular

tolerability was excellent and no triptan-like events such as chest symptoms were reported. This selective 5-HT$_{1F}$ receptor agonist has a high incidence of moderate or severe adverse central nervous system-related events, such as dizziness, fatigue, vertigo, somnolence, and paraesthesia [45,46].

Although it appears to be effective, its rather large range of such central side-effects may hinder its further development.

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 [47]. 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 GPCRs. 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 [48].

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 [49].

D1 and D2 dopamine receptors can be found in the rat TRIG, mesencephalic trigeminal nucleus and trigeminocervical complex [50,51], 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 [52] and DRD4 polymorphism [53] in migraine without aura. A decreased allelic distribution of dopamine-β-hydroxylase polymorphism was also observed, accompanied by an increased dopamine level in migraineurs [54].

4.1 Prochlorperazine
The intravenous administration of prochlorperazine (5 – 10 mg) led to a response rate of 88%, as compared with 45% for placebo. The headache relief duration was 30 min [55]. 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 [56].

4.2 Chlorpromazine
Chlorpromazine relieved pain, nausea, and phono- and photophobia in 1 h (95%) in an intravenous dose of 0.1 mg/kg [57]. The main side-effects were postural hypotension, drowsiness, and akathizia [56].

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 [58]. The standard dose is 5 – 20 mg for both oral and intravenous administration [56].

4.4 Domperidone
Domperidone is a peripheral DRD2 antagonist, because of its poor blood-brain barrier penetration. In a 20 – 30 mg dose, combined administration with 1000 mg paracetamol decreased the duration of migraine attacks by 30% [59]. 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 [60]. No side- effects were published.

4.5 Haloperidol
Significant migraine pain relief was observed in 80% of migraineurs after intravenously administered haloperidol (5 mg) [61]. The main adverse events were sedation and akathisia [56,61].

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 [62]. Droperidol is also contraindicated in the event of a long QTc interval [56].

It should be emphasized that these D2-dopamine receptor antagonists decrease only the premonitory symptoms of migraine, although they also have the capability to alleviate the headache in combination treatment by ameliorating the gastric absorption. They have severe unfavorable side-effects, as they can additionally act via serotonergic, cholinergic, adrenergic, histaminergic. or even calcium channels [63,64]. The development of specific pharmacons appears necessary.

5. Pituitary adenylate cyclase-activating polypeptide type 1 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 [65]. 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 [66]. PACAP-38 does not pass the blood-brain barrier as it is a large molecule [67]. The plasma elimination half-life of PACAP-38 is < 5 min [68].

Immunohistochemical studies have demonstrated the expression of PACAP in the parasympathetic and sensory ganglia [8,12,69], the human TNC and the C1 and C2 levels of the cervical spinal cord [70].

Schytz *et al.* observed 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 [71,72]. PACAP-38 infusion caused a pronounced dilatation of the extracranial, but not the intracranial arteries. The median time to attack onset was 4 h 15 min after the administration of PACAP38 infusion. The other interesting point was that the median peak headache intensity was 4 on the verbal rating scale (range 0 – 9), while the median time to peak headache occurred 2 h 45 min after the drug administration [73]. It is noteworthy that another member of this neuropeptide superfamily, VIP, did not induce migraine-like headache on intravenous administration [74] and the VIP-induced dilation was normalized in a shorter period (after 2 h) relative to PACAP-38- induced vasodilation. The possible role of PACAP-38 in migraine attack initiation is emphasized by the observation of an increased plasma PACAP-38 level 1 h after the PACAP-38 infusion only in those patients who later report migraine attacks. This suggests the possibility of *de novo* synthesis or release of PACAP-38 during migraine [73]. 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 [75].

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 [76]. Until now, only one PAC1 receptor agonist (maxadilan) is available, which was isolated from the 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 [77]. 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 [78]. 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. 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 [13,79,80]. Animal studies revealed the presence

of glutamatergic neurons in the TRIG [40], and dural and trigeminal nerve stimulation increased the level of glutamate in the TNC [81,82]. In human studies, an elevated level of glutamate was observed in the cerebrospinal fluid [79], the plasma, and the saliva [80] 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, AMPA, and kainate [83]. 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 coagonist glycine or D-serine is needed [84]. 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 [85]. NMDA receptors are expressed in the superficial laminae of the TNC in rat [86], in the TRIG [87] and in the thalamus [88], and they are also involved in central sensitization [89].

Cortical spreading depression (CSD) is a propagating transient negative direct potential shift, which occurs in migraine with aura [90]. Elevation of the extracellular concentration of K^+ is a potent trigger of CSD [91]. The inhibition of this process by NMDA receptor antagonists emphasizes the action of glutamate in the initiation of CSD [92].

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

6.1 Classical NMDA receptor antagonists
6.1.1 MK-801
MK-801, a noncompetitive 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 [93], to inhibit CSD [94], and to decrease the neurogenic dural vasodilation [95], but to increase the neuronal activity in the descending antinociceptive system (the ventrolateral periaqueductal grey matter (PAG), nucleus raphe magnus (NRM), dorsal raphe nucleus, and Edinger-Westphal nucleus) [96]. 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 [97]. Human immunohistochemical studies revealed CGRP, PACAP immunoreactive fibers, and neurons in the LC, and substance P afferentation in the PAG and RNM [98]. These observations suggested that these specific nuclei influence the activation of TNC. Human Phase I studies are required.

6.1.2 Memantin
Memantin is another noncompetitive NMDA receptor blocker, with an effect of CSD prevention [92]. In a clinical study, memantin in a dose of 10 – 20 mg was effective as preventive treatment of refractory migraine, as it significantly decreased

the monthly headache frequency and the mean disability score [99]. On the other hand, 37.5% of the patients reported side-effects, such as somnolence, asthenia, anxiety, depression, and an increase in weight [99].

6.1.3 L-701,324

L-701,324 is an NMDA glycine-site antagonist. On systemic administration, it inhibited CSD in rats [100].

6.1.4 Ketamine

Ketamine, a noncompetitive NMDA receptor antagonist, reduced neurogenic dural vasodilation in an experimental model [95]. 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 [101].

6.2 Endogenous NMDA receptor antagonists
6.2.1 Kynurenines

Kynurenic acid (KYNA) is one of the very few endogenous NMDA receptor antagonists [13,102]: 40% is produced locally in the central nervous system, while the remaining 60% is taken up from the blood [103]. KYNA (4-hydroxyquinoline-2-carboxylic acid) is produced from L-kynurenine (L-KYN) by neurons and astrocytes [104]. At 7.9 μM, KYNA effectively inhibited the NMDA receptors via attachment to the glycine-binding site [105]. It is to be noted that KYNA has a concentration-dependent neuromodulatory effect, as a Janus-faced compound. In a nanomolar concentration it facilitates, while in a micromolar concentration it inhibits the NMDA and AMPA receptors [106,107].

KYNA influences pain transmission via second-order neurons in the TNC and can modulate pain control through the brainstem 'migraine generators'. There are data which highlight the connection between kynurenines and CSD. Under experimental conditions, the administration of L-KYN, KYNA, and a KYNA derivative suppressed CSD [108,109]. Because of the poor blood-brain barrier penetration of KYNA [110-112], synthetic KYNA analogues that cross the blood-brain barrier much more readily are needed for a human Phase I study.

7. Conclusion

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 antimigraine agent which has 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 single therapy influenced only the premonitory symptoms of migraine, and not headache pain. 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

A crucial condition of good clinical practice is evidence-based therapy, which demands a knowledge of the exact pathomechanism of the disease. The most critical point of migraine attack therapy at present is that the precise pathomechanism of migraine is still lacking. Numerous working hypotheses have postulated possible sites of the initiation of the migraine attack, such as neuronal or vascular, peripheral (TRIG) or central (central nervous system), cortical or distinct brainstem nuclei, and the debate continues. Nevertheless, some basic physiological processes have been established. Among them, the peripheral and central sensitization of the first-, second-, or third-order neurons may explain the throbbing nature of the headache, worsening the headache pain during physical activation, or cephalic and extracephalic allodynia. The phenomenon of CSD, which is a slowly progressing wave (3 – 5 mm/min) of neurono-glial depolarization, may lie behind the aura phase of migraine. The activation or inhibition of different receptor subclasses, for example, CGRP, 5-HT, PACAP, glutamate, or dopamine, might explain the pain transmission and the concomitant clinical symptoms of migraine attack. On the other hand, these observations do not explain the whole process of the migraine attack. Moreover, the genetic background is still unexplored in most migraine types. Nevertheless, an appropriate experimental animal migraine model does not exist, which impedes the development of causative pharmacotherapy.

This situation raises difficulties in the daily clinical practice. Both patients and neurologists seek the attainment of rapid and complete relief from the pain and associated symptoms with safety, good tolerability, an excellent pharmacokinetic, and a low side-effect profile, with simple administration and a low price.

The recent gold standard of acute migraine therapy has been the use of triptans. The problem is that they do not cover the overall population of migraineurs and they cannot be used in patients with overt cardiovascular disease or a high cardiovascular risk. In view of the role of CGRP in the hypothesis of TS and in order to avoid the triptan side-effect profile, the CGRP-RAs (gepants) have been developed and demonstrated high efficacy in studies. The only disadvantages were the route of administration and liver toxicity, through these occur only

on long-term and frequent use. The newly synthesized CGRP-RAs have highly potent and selective pharmacological profiles and are of great promise for the coming years. In this review we discuss the acute therapy of migraine, but we also stress the recent pharmacological research which has led to a novel target for the prophylactic treatment of migraine with humanized monoclonal antibodies against CGRP and the CGRP receptor [113]. LY2951742, ALD403, and LBR-101 have been developed against CGRP. Currently the only anti-CGRP receptor monoclonal antibody is AMG 334. These compounds have undergone Phase I and II studies of episodic state and chronic migraine. They have favorable efficacy and good tolerability profiles with low side-effects [113-115]. The CGRP theory is weakened by human biochemical observations that numerous other factors such as orexin, endothelins, adipokines, leptin, neurotrophins, and endocannabinoids can vary in migraineurs. The ultimate goal is to find a specific biomarker for migraine which can be used in everyday clinical practice for the diagnosis of migraine and its correct treatment.

As regards the neuronal hypothesis of migraine, a highly selective 5-HT$_{1F}$ receptor agonist has been developed and its efficacy lends strong support to this theory. In the near future, the need is to find a balance between the high efficacy and the unfavorable side-effect profile.

During the research of receptor-specific antimigraine therapy, the possible roles of DRD2 and NMDA receptors have emerged. The currently available DRD2 antagonists are antiemetics or have been used in psychiatric disorders for decades. In this area we still lack specific drug candidates, and hence the development of such agents may be useful for attack therapy. As concerns the NMDA site, there is no or very little clinical evidence of an effect; the available data relating to CSD are from animal experiments. This disadvantageous situation should be modified in coming clinical studies.

The ongoing research into migraine attack therapy is very intense. In this particular area PACAP and the kynurenines are among the most promising target candidates. No drugs, are yet at hand, but in theory the function of the PAC1 receptor might be important. The goal is to develop a PAC1 receptor antagonist. On the other hand, KYNA is among the few endogenous NMDA receptor antagonists which is connected with the pathomechanism of migraine, for example, in pain transmission and CSD. In order to organize a proof-of-concept human study, the development of their synthetic analogues that readily cross the blood-brain barrier is required.

All of the aforementioned molecules have certain beneficial characteristics, but more development and Phase studies are needed for their final evaluation.

Declaration of interest

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