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REVIEW ARTICLE

The Therapeutic Impact of New Migraine Discoveries

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Abstract: ***Background:*** Migraine is one of the most disabling neurological conditions and associated with high socio-economic costs. Though certain aspects of the pathomechanism of migraine are still incompletely understood, the leading hypothesis implicates the role of the activation of the trigeminovascular system. Triptans are considered to be the current gold standard therapy for migraine attacks; however, their use in clinical practice is limited. Prophylactic treatment includes non-specific approaches for migraine prevention. All these support the need for future studies in order to develop innovative anti-migraine drugs.

Objective: The present study is a review of the current literature regarding new therapeutic lines in migraine research.

Method: A systematic literature search in the database of PUBMED was conducted concerning therapeutic strategies in a migraine published until July 2017.

Results: Ongoing clinical trials with 5-HT_{1F} receptor agonists and glutamate receptor antagonists offer promising new aspects for acute migraine treatment. Monoclonal antibodies against CGRP and the CGRP receptor are revolutionary in preventive treatment; however, further long-term studies are needed to test their tolerability. Preclinical studies show positive results with PACAP- and kynurenic acid-related treatments. Other promising therapeutic strategies (such as those targeting TRPV1, substance P, NOS, or orexin) have failed to show efficacy in clinical trials.

Conclusion: Due to their side-effects, current therapeutic approaches are not suitable for all migraine patients. Especially frequent episodic and chronic migraine represents a therapeutic challenge for researchers. Clinical and preclinical studies are needed to untangle the pathophysiology of migraine in order to develop new and migraine-specific therapies.

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1. INTRODUCTION

1.1. Migraine

Migraine is a severe neurological condition, ranked as the sixth most disabling condition of all illnesses and the most disabling condition of neurological diseases, based on the results of the Global Burden of Disease Study [1]. Clinically, the earliest signs of a migraine attack include non-specific premonitory symptoms such as tiredness, concentrating difficulty and depression, symptoms related mainly to the activation of the hypothalamus [2]. Visual aura can precede or even accompany a headache, represented predominantly by a blind or scintillating scotoma [3-4]. Other non-visual

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auras (*e.g.,* sensory, olfactory, or temporary motor symptoms) might also occur [5-6]. In the headache phase, the pain is usually unilateral, throbbing, severe or moderate in intensity, aggravated by physical activity, which is often accompanied by nausea, vomiting, and photophobia [7]. Postdrome symptoms are consistent with those in the premonitory phase, including physical and mental tiredness, depressed mood and muscle stiffness [8-9].

Despite numerous studies that have tried to shed light on the pathomechanism of migraine, several aspects are still unclear. The leading hypothesis implicates the role of the activation of the trigeminovascular system. Dural perivascular nerve endings that originate from the neurons of the trigeminal ganglion (TG) represent the primary sensory neurons of the pathway. The neuronal cell bodies within the TG are surrounded by satellite glial cells. The second-order neurons are located in the trigeminal nucleus caudalis (TNC) and C_1-C_2 region of the spinal cord [10]. They connect pain signals to the thalamus and the cerebral cortex [10-11]. Structural and functional brain imaging studies have revealed a number of other brain areas that become activated during migraine attacks, such as the nucleus raphe magnus (NRM), the nucleus raphe dorsalis (DG), the periaqueductal grey matter (PAG), and the locus ceruleus (LC) [12-13]. Structural alterations of the brain have been noted in areas involved in pain processing, such as the anterior cingulate cortex or the trigeminal system [14]. The origin of migraine pain is still a question of debate. Imaging studies showed no vasodilation of intracranial and extracerebral arteries, rendering the vascular theory of Wolff obsolete [15]. One of the theories postulates that the above mentioned brainstem nuclei are responsible for the initiation of migraine pain; therefore, they are sometimes referred to as 'migraine generators'. It is still a question whether activation of these brain areas generates the pain sensation or they become activated secondarily. Neurogenic inflammation is hypothesized to be an important factor in migraine pathophysiology. It is thought to induce a state of hyperexcitability, as nociceptive signals are transported ortho- and antidromically, leading to the release of various cytokines and neuronal messenger molecules (such as calcitonin gene-related peptide (CGRP), substance P (SP), neuropeptide Y (NPY), and nitric oxide (NO)). These molecules are presumed to induce the activation of immune cells, mast cells, and astrocytes and lead to vascular changes that might evoke blood-brain barrier (BBB) dysfunction [16-17]. Descending neurons of the CNS might aggravate the inflammatory responses, resulting in long-term potentiation (LTP) [17-18]. Another phenomenon that has been under investigation as an initiating component of the migraine pain process is cortical spreading depression (CSD). CSD is a depolarization wave that moves across the cortex from the occipital lobe towards the frontal areas, and has been suggested to represent the electrophysiological correlate of the aura phase of migraine; however, CSD alone is neither sufficient nor necessary to trigger migraine attacks [19-20]. Although extensive efforts have been made to elucidate the possible mechanisms that play pathogenic roles in migraine, certainly much is yet to be unveiled to correctly interpret this disease. The most relevant contemporary concept postulates that migraine is a neurovascular disorder. We hypothesize that pain originates in the central nervous system (CNS), resulting in hypersensitivity of the perivascular nociceptive afferent nerve fibers, which play an essential role in the pathogenesis.

1.2. Current Treatments in Migraine

Regarding migraine treatment, analgesics (NSAIDs), antiemetics and triptans are the drugs to be chosen in the case of a migraine attack. The current gold standard therapy is the use of triptans, drugs with serotonin receptor ($5\text{-}HT_{1B/1D}$) agonist properties. The efficacy of triptans in migraine attacks has been proven in large placebo-controlled clinical trials [21]. They have proven efficacy in 60% of migraine attacks [22]. In clinical practice, the use of triptans has some limitations: clinical trials showed pain relief in only 28-59% of the patients [23]. They should be taken in the early phase, which leads to frequent drug intake and thus increased risk of chronification [24]. Frequent use of analgesics or triptans might lead to medication overuse headache (MOH). Other important requirements are related to the side-effects, to the safety and tolerability profiles [25]. One of the most important problems with triptans is related to their side effects. Following sumatriptan therapy, severe cardiovascular adverse events (such as stroke, myocardial infarction, and cardiac arrhythmias) have been reported to occur with an incidence of 1:1.000.000 [26-27]. Prophylactic therapy of migraine includes beta-adrenergic receptor blockers, calcium ion channel blockers, antiepileptic drugs, and antidepressants. Chronic migraine represents a therapeutic challenge because triptans can be used only 9 days/month due to high risk of chronification [24]. Lately, botulinum toxin A (BoNTA) injected intramuscularly into the muscles of face and head has proven to be efficient in chronic migraine [28-30].

Table 1. Pharmacological data for triptans (source: Tajti *et al*., 2015). IUPAC- International Union of Pure and Applied Chemistry, p.o.-per oral, s.c-subcutaneous [2

Drug name	Sumatriptan	Eletriptan	Zolmitriptan	Rizatriptan
Systematic (IUPAC) name	1-[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]-N-methyl-methanesulfonamide	(R)-3-[(-1-methylpyrrolidin-2-yl)merhyl]-5-(2-phenylsulfonethyl)-1H-indole	(S)-4-({3-[2-(dimetylamino)ethyl]-1H-indol-5-yl}metyl-1,3-oxazolidin-2-one	N,N-dimethyl-2-[5-(1H-1,2,4-triazol-1-ylmetyl)-1H-indol-3-yl]ethanesulfonamide
Route of administration	p.o., s.c., nasal, rectal, transdermal	p.o.	p.o., nasal	p.o.
Cmax	54 ng/ml (50-100 mg tablet)	188-234 ng/ml (80 mg tablet)	5.6-9 ng/ml (5mg tablet)	15.7 ng/ml (10 mg tablet)
Tmax	1.5 h (50-100 mg tablet)	1.8-2.5 h (80 mg tablet)	1.5 h (5mg tablet)	2.3 h (10 mg tablet)
$T_{1/2}$	2.3 h (50-100 mg tablet)	4-7 h (80 mg tablet)	2.7 h (5mg tablet)	3.2 (10 mg tablet)
Metabolism	Hepatic-MAO	Hepatic-CYP-34A	Hepatic-CYP1A2	Hepatic-MAO
Excretion	Renal, fecal	Hepatic	Renal, fecal	Renal, fecal

The future goal should be the development of migraine-specific drugs with good safety and tolerability profile [31]. Due to the individual pain sensation of the patients, therapy should aim at personalized medicine. The difficulty of developing new migraine-specific drugs is represented by the lack of adequate animal models and specific biomarkers [25].

2. NEW THERAPEUTIC TARGETS IN MIGRAINE

In the present article, we have aimed to assess the current and novel therapeutic strategies related to different neuropeptides and molecules putatively involved in the pathomechanisms of migraine. A systematic literature review was performed in the database of PUBMED until July 2017. We used the following search strings: "migraine", "migraine treatment", and "clinical studies in migraine".

2.1. 5-hydroxytryptamine (5-HT, Serotonin)

5-HT is a metabolite of tryptophan that has proven to play a pivotal role in migraine because elevated levels of its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) were detected early in the plasma of migraine patients during attacks [32]. Numerous studies related to 5-HT led to the discovery of triptans, which at present represent the gold standard therapy in the acute treatment. Early studies suggested a vasoconstrictor effect on the cranial arteries [33-36]; however, it has been demonstrated lately that triptans are not only cerebral and dural vasoconstrictors but they also exert neuronal effects. Indeed, triptans act on neurogenic inflammation in the dura mater [37-38] and they also modulate the activity of trigeminal neurons [39]. 5-HT receptors represent one of the most complex families of neurotransmitter receptors, having seven subfamilies and a lot of subtypes. Except for 5-HT_3, all forms are parts of the G protein-coupled receptor (GPCR) superfamily [40]. Several hundreds of genes encode different receptors for neurotransmitters, and post-translational modifications result in different proteins [41]. More than one hundred cloned orphan GPCRs have so far been identified, and it is still unknown how many of them belong to the 5-HT receptor family. In an attempt to reduce the cardiovascular side effects of triptans, researchers focused on finding potent and selective ligands for the different receptor subtypes. Sumatriptan and naratriptan have been shown to bind with high affinity to the 5-HT_{1F} receptor [42], a subtype of the 5-HT_1 receptor class consisting of 366 amino acids and having 7 transmembrane domains (TMD) [43-44]. 5-HT_{1F} receptors have been shown to be expressed in glutamatergic neurons of the trigeminal system and also in the cerebral vessels, with no vasoconstrictor effect [45-46]. The ability of 5-HT_{1F} receptors to modulate trigeminal responses without any effect on the vascular tone made 5-HT_{1F} agonists promising tools as innovative anti-migraine drugs [47-48]. 4-Fluoro-N-[3-(1-methyl-4-piperidinyl)-1H-indol-5-yl]-benzamide (LY334370) has been shown to be a high-affinity agonist of the 5-HT_{1F} receptor [49]. Among other 5-HT receptors, LY334370 shows the next highest affinity for 5-HT_{1A} and 5-HT_{1E}, binding only a small fraction of these receptors [50]. In preclinical studies, LY334370

has been proven to block neurogenic inflammation [49] and diminished c-fos immunopositivity in the TNC, without any vasomotor effect on cerebral vessels [51-52]. In clinical studies, LY334370 was tested in three different doses. The 60 mg and 120 mg doses showed superiority over placebo at all three endpoints (2 h response, 2 h pain-free, sustained effect) with no cardiovascular side effects [53]. Although the study proved the efficacy of LY334370 for acute treatment, the studies were cancelled due to liver toxicity following long-term use in animal models.

2,4,6-Trifluoro-N-[6-[(1-methylpiperidin-4-yl)carbonyl]pyridin-2yl]benzamide (lasmiditan) represents a new generation of 5-HT_{1F} agonists. Lasmiditan does not contain the indole core that is present in 5-HT and triptans, as the indole core is replaced by a pyridinoyl-piperidine scaffold. Lasmiditan has higher selectivity to the 5-HT_{1F} receptor than LY334370. Following oral lasmiditan administration, decreased c-fos activation was detected in TNC in a model of electrical stimulation of rat TG and no vasoconstrictive effect was noted [54]. Furthermore, lasmiditan, in contrast with triptans, can penetrate the BBB, suggesting to be able to act on central mechanisms [55]. Phase 1 and phase 2 clinical trials have been carried out to test the intravenous and oral efficacy of lasmiditan [56-57]. Lasmiditan has proven superiority over placebo in the primary endpoint of headache response, with a linear dose-response relationship [56]. Oral administration in a dose of 400 mg showed higher therapeutic gain compared to the intravenous dose of 20 mg [57]. The studies show rapid absorption and a bioavailability of 40% in the case of oral administration [58]. Two ongoing phase 3 and a long-term open-label trial were started in 2015 to test lasmiditan in episodic, disabling migraine [55]. Due to its different chemical structure and the selective action on the 5-HT_{1F} receptor, the side effects of lasmiditan are completely different from those of triptans. Dizziness, paresthesia, and vertigo were the most common adverse events reported, predominantly attributable to the presence of 5-HT_{1F} receptors in the cerebellum and the vestibular nuclei, and also because of the high BBB penetration of lasmiditan [55, 58]. On the basis of these, CNS-related side effects can be anticipated following a long-term use of lasmiditan, which might limit its clinical use and delay further studies [59].

NXN-188 is an oral drug developed with a dual mechanism of action: acting on neuronal NO synthase (nNOS) enzyme and having a high affinity for the 5-$HT_{1B/1D}$ receptor. Preclinical studies have demonstrated the ability of this molecule to inhibit CGRP release in animal models using capsaicin or an electrical stimulation of the trigeminovascular system. NXN-188 itself did not induce any vasoconstriction in the middle meningeal artery (MMA) but blocked capsaicin-induced vasodilation. GR127935, a 5-$HT_{1B/1D}$ receptor antagonist was able to block the effect of sumatriptan on the MMA and did not influence the effect of NXN-188, suggesting that the novel compound acts partially on nNOS, being a promising future therapeutic approach for migraine prophylaxis [60]. Regarding clinical studies, five phase 1 trials have been carried out in order to test the safety and assess the pharmacokinetics of NXN-188 in healthy volunteers. The compound had two absorption phases: the first peaked at 1 h, and the second at 4-5 h. Initial elimination from the plasma was rapid (plasma concentration decreased with 70-90% of the C_{max} within 24 h) followed by a prolonged elimination (with 1-5% of the C_{max}) for several weeks. NXN-188 was well tolerated by the participants, the reported adverse events were dizziness, headache, and somnolence [61]). Unfortunately, phase 2 clinical trials showed no statistically significant effect on migraine with aura compared to placebo [62].

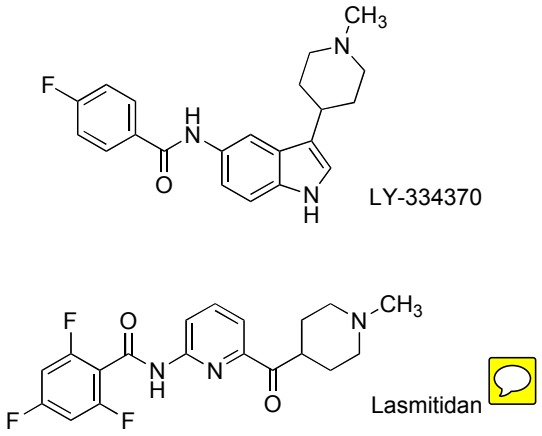

Fig. (1). Chemical structure of LY-334370 and Lasmiditan.

2.2. Glutamate (Glu)

Glu, the major excitatory neurotransmitter in the CNS, has been shown to play crucial roles in the pathophysiology of migraine. Elevated levels of Glu were detected in the serum of migraine patients [63] and in the cerebrospinal fluid (CSF) of patient affected by chronic migraine [64]. Glu mediates the CSD phenomenon [65] and has been shown to be co-released with CGRP from the neurons of the TG upon activation [66]. In animal models of trigeminovascular activation, increased Glu activity was detected [67-68]. Glu acts on ionotropic and metabotropic receptors as well [69]. The ligand-gated ion channels are the *N*-methyl-D-

aspartate (NMDA) receptors, the α-amino-3-hydroxí-5-methyl-4-isoxazelopropionic acid (AMPA) receptors and the kainate receptors (that can be divided into several subtypes), which mediate fast synaptic transport [70]. AMPA receptors have four semiautonomous domains: the amino-terminal domain, the extracellular ligand-binding domain (LBD), the TMD, and the intracellular carboxyl-terminal domain (CTD) [70-71]. NMDA receptors contain three subunits: NR1 is common in all cell types; NR2 has four subtypes differentially expressed in different cell types and in various CNS structures during certain development processes; and NR3 with modulatory function on the receptor. For optimal function, both the NR1 and the NR2 subunits need to be expressed. The NR1 subunit contains the glycine (Gly)-binding site. Gly acts as a coagonist of Glu and is essential for the activation of the receptor. In inactive form at the resting potential, the channel is blocked by Mg^{2+}. Following activation by binding of both Glu and Gly to the receptor, Mg^{2+} dissociates from the receptor and opens the channel, resulting in the flow of Na^{+} and Ca^{2+} into and K^{+} out of the cell. The Ca^{2+} signal then activates various intracellular pathways that lead to exocytotic effects [72-73]. All three ionotropic receptors play pivotal roles in migraine, acting on neuronal activation and signal transmission in the trigeminal system, but the only receptor linked to CSD and thus the aura phenomenon is the NMDA receptor [74]. Metabotropic Glu receptors (mGluRs) are GPCRs and contain at least eight receptor subtypes [75]. The N-terminal domain, called Venus Flytrap Domain, contains two lobes. The binding of the ligand leads to the closure of the two lobes, leading to the activation of the receptors [76]. The seven TMD of mGluRs is rich in cysteine, which forms disulfide bonds in order to increase the stability of the domain [77]. The CTD is close to the cell membrane and interacts with signaling pathways [75]. In a small study on familial hemiplegic migraine (FHM), intranasal administration of ketamine, an NMDA receptor antagonist that acts on the Glu-binding site, reduced the intensity and duration of motor symptoms in almost half of the patients [78]. In a phase 2 study with migraine patients suffering from prolonged aura, intranasal ketamine was able to reduce the severity of aura but did not influence its duration [79]. The AMPA/kainate receptor antagonist, tezampanel (LY293558), and a kainate receptor antagonist, LY 466195, were shown to decrease c-fos activity in the rat TNC following electrical stimulation of the TG; whereas the AMPA receptor antagonist LY300178 did not influence c-fos activation [80]. This leads to the conclusion that the effect of tezampanel might be mediated through the kainate rather than the AMPA receptor. A phase 2 clinical trial demonstrated that intravenous tezampanel was superior to placebo in all endpoints (sustained relief of pain and other associated symptoms) and no cardiovascular side effects were noted. Adverse events were mainly CNS-related, including dizziness and somnolence [81]. For LY466195, intravenous doses of 1 and 3 mg were compared with placebo. The 1 mg dose was not effective whereas the 3 mg dose showed superiority compared to placebo. As adverse effects, visual disturbances were reported in 21% of the patients [82]. ADX 10059, a negative allosteric modulator of the mGluR5, was also tested in phase 2 clinical trials for acute migraine therapy. Following oral administration of ADX 10059, pain relief was significantly higher than in the placebo group at the primary endpoint (2 h), but this effect was not proven to be sustained. As side effects, dizziness, vertigo, and visual disturbances were reported [74, 83]. All these data suggest that modulation of glutamatergic neurotransmission might represent an important mechanism for innovative drugs in both the acute and the prophylactic treatments of migraine. Following the contemporary concept, kainate receptor antagonist might represent an effective therapeutic modalities for acute treatment, whereas specific NMDA receptor antagonists might be promising therapeutic tools for aura phenomena.

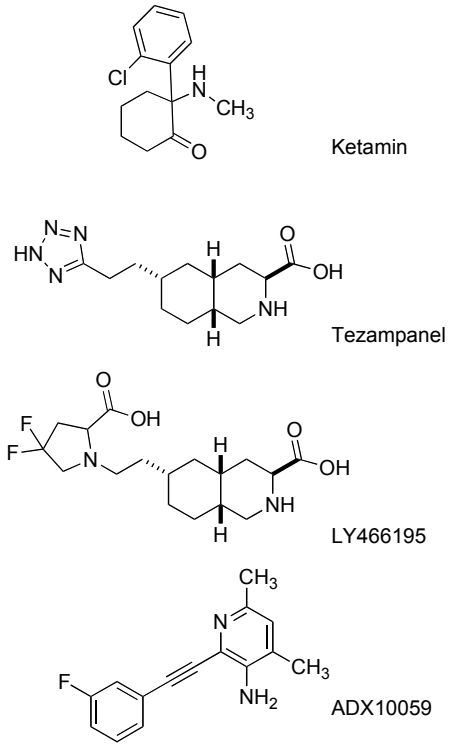

Fig. (2). Chemical structure of Glu related therapeutic targets.

2.3. Calcitonin Gene-related Peptide (CGRP)

The pivotal role of CGRP in migraine has been suggested for decades [84-85]. CGRP is a 37-amino-acid peptide that has two isoforms, αCGRP and βCGRP, with similar chemical structures and biological functions, encoded by two different genes on chromosome 11 in humans [86]. αCGRP, expressed predominantly in the nervous system, is encoded by the CALCI gene (together with calcitonin) by means of an alternative splicing mechanism. Expression of exons 5 and 6 leads to the production of αCGRP mRNA, which is translated to a prohormone of 121 amino acids and cleaved secondarily to yield the mature protein [87]. βCGRP is expressed in the enteric nervous system and is transcribed from the CALCII gene [88]. The CGRP receptor is part of the GPCR superfamily and consists of a 7-TMD, called calcitonin receptor-like receptor (CLR), and a single-transmembrane spanning protein, called receptor activity-modifying protein 1 (RAMP1), which is necessary for the binding of CGRP to the receptor [89]. The third component, called receptor component protein (RCP), does not affect the binding of CGRP to the receptor but it is necessary for signal transduction [90]. Previous studies have demonstrated that CGRP is a key mediator in migraine, as elevated levels of CGRP were found in the plasma, CSF and saliva of migraine patients [91-93]. Subsequently, mapping of CGRP and its receptors in different structures of the rat and human brain demonstrated their role in nociceptive transmission [94-96]. In animal models of trigeminovascular activation, increased CGRP activity was detected [97-99]. All these findings support a well-established position of CGRP in migraine pathophysiology and current efforts pursue the identification of potent anti-migraine drugs targeting CGRP and its receptors. The most comprehensively studied compounds were the 'gepants', acting on CGRP receptors. Olcegepant (BIBN 4096BS, 1-[3,5-Dibromo-N-[[4-(1,4-dihydro-2-oxo-3(2H)-quinazoline)-1-piperidinyl]carbonyl]-D-tyrosyl-L-lysyl]-4-(4-pyridyl)-piperazine) was the first CGRP receptor antagonist, binding with high selectivity to the CGRP receptors. Its relatively high molecular weight (Mw = 870 Da) and low oral bioavailability necessitated an intravenous route of administration. In animal models, olcegepant has proven to decrease CGRP-mediated trigeminal activation [100]. In phase 1 clinical study, the maximal concentration was dose-proportional (C_{max} = 0.87 mg/ml), the biological half-life ($T_{1/2}$) was 2.5 h and no serious adverse events were noted (the most common included fatigue and paresthesia) [101]. Although phase 2 clinical trials supported the efficacy of olcegepant and, apart from paresthesia, no severe adverse events were noted, [102] the intravenous route limited its use in the daily clinical practice [103]. Therefore, an oral formula was developed, referred to as telcagepant (MK-0974, N-((3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl)-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide). In animal models, telcagepant did not show any effect on the diameter of cranial arteries, but blocked the effect of CGRP [104]. Human studies showed rapid absorption of telcagepant, with a $T_{1/2}$ of 6 h and C_{max} of 0.55 mg/ml. In phase 2 clinical trials, telcagepant in 300-600-mg doses showed superiority to placebo and the same efficacy as zolmitriptan (5 mg). Unfortunately, the development of telcagepant and its successor, MK-3207, was stopped due to liver toxicity and elevated gamma-glutamyltransferase (GGT) levels developed after long-term and frequent administration [105]. It has been suggested that hepatotoxicity might be a side effect related to one of the metabolites of the compounds [106]. Rimagepant (BMS-927711, (5S,6S,9R)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyridin-9-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate) and BI 44370 TA (4-[[(7R)-8-cyclopentyl-7-ethyl-5-methyl-6-oxo-7H-pteridin-2-yl]amino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide) have proven efficacy compared to placebo in phase 2 clinical studies without any adverse event related to liver toxicity; however, the one-dose design of the trials offered limited information regarding the safety profile in case of repeated treatment [107-108]. A newly designed compound, ubrogepant, (MK-1602, (3'S)-N-((3S,5S,6R)-6-methyl-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-yl)-2'-oxo-1',2',5,7-tetrahydrospiro(cyclopenta(b)pyridine-6,3'-pyrrolo(2,3-b)pyridine)-3-carboxamide) has recently been developed for acute treatment of migraine and has demonstrated superiority to placebo with a good safety and efficacy profile [109]. A phase 3 clinical study is currently recruiting participants. We await further studies providing detailed assessment of the tolerability profile during long-term use.

New classes of biological therapies, monoclonal antibodies acting on CGRP or its receptors have been developed in recent years. The mechanism of action of these molecules is still not fully understood; however, they have been shown to prevent repeated activation of the trigeminovascular system induced by CGRP, reducing headache frequency [110]. The pharmacokinetic and pharmacodynamic properties of these molecules differ completely from those of the gepants. Due to their high molecular weight (150 kDa), their instability

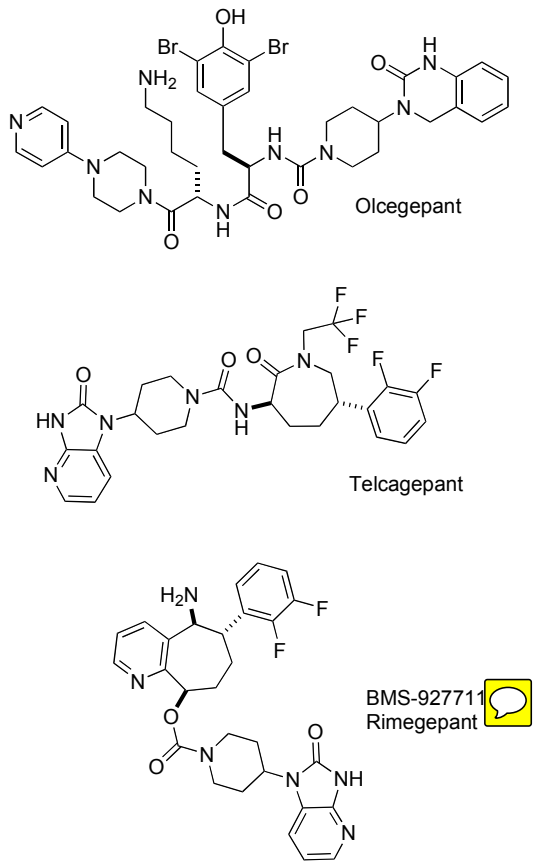

Fig. (3). Chemical structure of CGRP receptor antagonists.

in the gastrointestinal tract, and the low permeability through cell membranes, these molecules can only be administrated subcutaneously or intravenously. These drugs are also not able to cross the BBB [111]. These facts collectively lead to the conclusion that these molecules act on peripheral targets such as the TG [112], as TG was proven to be placed outside the BBB [94]. Their plasma half-life is extended to days and weeks. This enables longer dosing intervals, which is rather favorable in terms of patient compliance [113-114]. As these molecules are metabolized to small peptides and amino acids, they do not affect hepatic or renal enzymes and the incidence of drug-drug interactions is very low [115]. They are potential immunogens; therefore, they might evoke various immunological adverse events such as hypersensitivity, immunosuppression or autoimmune processes [116-117]. Although the studies performed with CGRP-related monoclonal antibodies have not revealed serious immunotoxic effects so far, a small percentage of the patients were positive for anti-drug antibodies [111]. These antibodies are of great importance as they might reduce future therapeutic efficacy and might aid the development of allergic reactions [111, 118]. Three of the monoclonal antibodies tested act on CGRP: ALD403 (eptinezumab), TEV-48125 (fremanezumab), and LY2951742 (galcanezumab) whereas AMG334 (erenumab) targets the CGRP receptor. All four antibodies have demonstrated positive effects in migraine prevention in phase 1 and phase 2 clinical trials, with no significant adverse reactions reported [119-122]. TEV-48125 might represent a promising target in chronic migraine as well [123]. There are small differences between the association/dissociation rates of the four antibodies that might have an impact on their efficacy: ALD403 attaches to the target twice as rapidly as TEV-48125. LY2951742 takes effect as an incomplete agonist with fast binding to the target and rapid dissociation [111].

Primary results of phase 3 clinical trials were presented on the International Headache Congress 2017 (IHC 2017), in Vancouver. PROMISE-1 study was designed to evaluate the effect of i.v. eptinezumab in the prevention of frequent, episodic migraine. Adult patients were included, receiving 300mg, 100mg, 30mg eptinezumab and placebo. Significant reduction in migraine days was reported in case of eptinezumab, maintained at similar levels for long-term (12 weeks). Two phase 3 studies (EVOLVE-1 and EVOLVE-2) for s.c. use of galcanezumab were performed. Doses of 120mg and 240mg were tested and both doses proved superiority for overall mean change in migraine headache days. The REGAIN trial was a 3-month study, performed for the same doses of s.c. galcanezumab in patients with a chronic migraine. Both doses were superior to placebo regarding the reduction of migraine headache days. Also, treatment with self-administrated galcanezumab was proven to be safe and well-tolerated. The STRIVE trial was designed to test the effect of s.c. use of erenumab, for a dose of 140mg and 70mg. Over 24 weeks significant reduction was reported in the impact of migraine on physical, social and emotional functioning of episodic migraine patients (Cephalalgia, Volume 37, Issue 1_suppl, September 2017).

Although additional long-term clinical studies are needed, it might be reasonably postulated that these anti-CGRP monoclonal antibodies represent a new and effective therapeutic line in migraine prevention. They can be considered revolutionary in the pharmaceutical treatment of migraine, especially in case of chronic migraine. The only obstacle in their way towards a wide clinical use might be their cost/benefit ratio, as the cost related to the manufacturing of monoclonal antibodies is rather high. It should also be considered, however, that migraine is among the priciest neurologi-

cal diseases in Europe [124] and an effective treatment might lead to reduced health care costs.

3. PROMISING FUTURE THERAPEUTIC TARGETS IN PRECLINICAL PHASE

3.1. Pituitary Adenylate Cyclase-activating Polypeptide (PACAP)

PACAP is a neuropeptide isolated from the hypothalamus in 1989 [125]. Two bioactive forms of PACAP are known: PACAP1-38 and PACAP1-27. PACAP1-38 is formed from a precursor (prepro-PACAP) by convertase enzyme. Two Arg residues are split by a carboxypeptidase and the remaining Gly residues are used to amidate the Lys residue to yield PACAP1-38. Another series of Gly Lys Arg of PACAP 1-38 allows further reactions, providing PACAP1-27 [126]. The two active forms of PACAP cross the BBB in different ways: PACAP1-27 enters via transmembrane diffusion attributable to its lipophilic property, whereas PACAP1-38 uses a carrier-mediated peptide transport mechanism [127]. The role of PACAP1-38 has been suggested in the ethiopathology of migraine, though some aspects are still yet to be revealed [128-130]. PACAP1-38 was detected in the TG [131], in the TNC [132], and also in the parasympathetic otic and sphenopalatine ganglia [133-134]. Elevated levels of PACAP were found in the interictal phase compared to the ictal phase in migraine patients and also in cluster headache attacks [135-136]. Intravenous infusion of PACAP was able to induce headache in healthy volunteers and evoke migraine-like attacks in patients suffering from migraine without aura [137-138]. Vasoactive intestinal peptide (VIP) and PACAP1-38 share the same receptors: VPAC1 and VPAC2, whereas PAC1 has higher affinity for PACAP1-38 [139-140]. The vasodilatory effect of PACAP1-38 on dural vessels has been proven to be mediated via VPAC2 receptors, whereas neurogenic dural vasodilation induced by electrical stimulation of the trigeminal nerve terminals is mediated predominantly by PAC1 [138, 141]. Central PAC1 receptors are suggested to play key roles in central trigeminal activation [142], as PACAP1-38 (but not VIP) has been shown to cause delayed sensitization of the trigeminal system. In an animal model of dural electrical stimulation, a BBB-impermeable PAC1 receptor antagonist was tested: in the case of peripheral administration, the substance was not able to prevent neuronal firing of the TNC, whereas the central (i.e. intraventricular) administration was able to decrease the neuronal activity [141]. To our knowledge, no PAC1 receptor antagonists are available that can penetrate the BBB. It is a question whether the peripheral action of these PAC1 receptor antagonists will prove sufficient to prevent migraine attacks or the development of novel small molecules will be needed with optimized BBB permeability. Another possibility to prevent PACAP1-38-initiated migraine attacks might be the use of monoclonal antibodies against PACAP1-38 per se or against PAC1 receptors, by analogy with those developed against CGRP and its receptor [143]. It is possible that new molecules are needed to also block the central action of PACAP1-38 via the PAC1 receptor in order to be effective against migraine attacks, whereas peripherally acting substances might be used as preventive therapies. Therapeutic strategies targeting PAC1 receptor represent promising approaches for the treatment of migraine, but further preclinical and clinical studies are warranted.

3.2. Kynurenic Acid (KYNA)

Tryptophan, one of the essential amino acids, is the precursor of 5-HT and L-kynurenine under physiological conditions. The kynurenine pathway has been previously presented in details [128, 144]. Briefly, it is a complex metabolic pathway with a lot of neuroactive products ending with NAD^+ [145]. As these neuroactive metabolites influence NMDA receptor-mediated excitotoxicity and the production of free radicals, they are presumed to play important roles in various diseases of the CNS [146-150]. KYNA acts on NMDA receptors binding to the Gly-binding site of the NR2 subunit [73] and it also acts on AMPA receptors with a dual action: in low concentrations it enhances, whereas in higher concentrations it decreases receptor activity [151-152]. This leads to the conclusion that modulation of the kynurenine pathway might represent an appropriate therapeutic tool in migraine treatment and is currently investigated in preclinical animal studies. As KYNA has a very low capacity to cross the BBB, different strategies are needed in order to take advantage of its anti-inflammatory and neuroprotective properties. One possibility could be the use of a prodrug such as L-kynurenine or its derivates [153-155]; whereas shifting the pathway towards the production of KYNA with different enzyme inhibitors would represent another possible therapeutic strategy [156-157]. During the last years, our research group has synthesized several different KYNA derivates that have proven to be effective in animal models of cerebral ischemia [158], Huntington's disease [159], epilepsy [160], and rat models of trigeminovascular activation [68, 161-162]. The chemical structures of these KYNA analogues have been previously presented. Briefly, a new cationic

center and a water-soluble side-chain were included in order to facilitate BBB penetration [163-164].

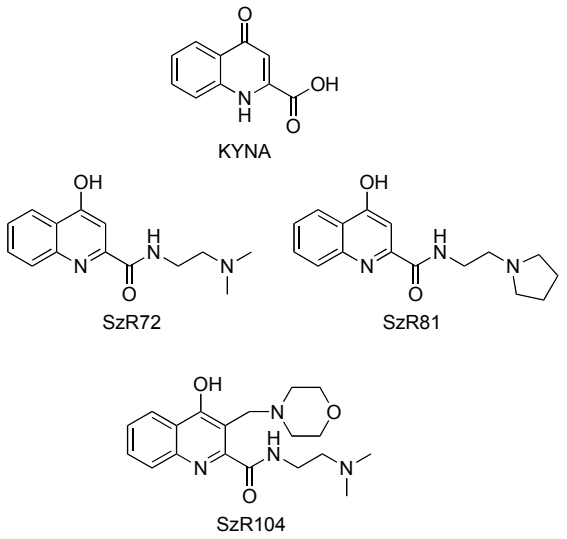

Fig. (4). Chemical structure of different KYNA analogues designed by our research group.

Their exact mechanism of action still needs to be untangled. There are two main hypotheses as regards their mechanism of action: 1) these molecules might act as analogues, mimicking some effects of KYNA, 2) they may dissociate into KYNA and serve as a prodrug [165-166]. Only a few studies are available to elucidate their pharmacokinetic profile. One of these focused on two KYNA derivates: N-(2-N,N-dymethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride (KA-1) and N-(2-N-pyrrolidinylethyl)- 4-oxo-1H-quinoline-2-carboxamide hydrochloride (KA-2). Following intraperitoneal treatment with these amides, the concentrations of KA-1, KA-2 and KYNA were measured in the rat serum and TNC. The study revealed that following intraperitoneal treatment with these amides, a sharp increase followed by a sudden decrease in the level of KA-1 and KA-2 in the serum could be detected. In the fifth hour, the compounds were still present in the serum. Although elevated levels of KYNA were found in the serum in the case of both molecules, the increase was less for KA-1 than for KA-2. In the CNS, only small amount of KA-2 was detected, with the level of KA-1 being below the lower limit of detection [165]. Although these KYNA amides were detected only in trace (or zero) amounts within the CNS, animal studies of trigeminovascular activation show decreased activation of the TNC following intraperitoneal treatment with KA1 [68, 167]. There are two potential explanations: 1. the two amids act peripherally, metabolized only in small proportion two KYNA, 2. the pharmacokinetic studies were performed in intact animals. In case of neurogenic inflammation, an important phenomenon that occurs during trigeminovascular activation causes BBB dysfunction, where the BBB becomes penetrable for substances that are normally unable to pass [17, 168]. We assume that during migraine attack the BBB dysfunction occurs and penetrance of KYNA analogues might be possible but future studies are needed to test this hypothesis.

In summary, all these data suggest that it is necessary to conduct further studies that are needed to enlighten the mechanism behind the positive effects of the KYNA amides.

4. FAILED THERAPEUTIC TARGETS

4.1. Vanilloid Receptor 1 (TRPV1)

TRPV1 is a non-selective cationic channel, which is sensitized and up-regulated during inflammation, playing an important role in noxious stimulatory states [169-170]. The efficacy of TRPV1 antagonists in preclinical models of chronic pain has suggested the potential therapeutic benefit of TRPV1 inhibition in this condition [171]. In case of migraine, animal studies provided contradictory results: a TRPV1 antagonist was ineffective in two different animal models [172], whereas another TRPV1 antagonist was proven to be effective in an animal model of electrical and mechanical stimulation of the dura mater in cats [173]. *In vitro* pharmacological studies suggested that SB-70498 had the best pharmacological properties among the TRPV1 receptor antagonists. Its metabolic stability and a bioavailability of almost 86% made SB-70498 a promising molecule for clinical studies [174]. However, phase 2 clinical studies were terminated early as SB-70498 did not show any superiority to placebo in acute migraine treatment [175]. These findings do not support the use of TRPV1 antagonists in the treatment of migraine.

4.2. Substance P (SP)

SP was shown to be expressed in various parts of the CNS and has been implicated in the pathophysiology of migraine [176]. SP acts on the tachykinin receptors (NK_1, NK_2, and NK_3), predominantly on NK_1. The SP receptor antagonist, PRP100893, has proven to diminish plasma protein extravasation following electrical stimulation of the TG in guinea pigs [177]. Unfortunately, phase 2 clinical studies did not support the efficacy of SP receptor antagonist in acute migraine attacks [178]. Lanepitant, another NK_1 receptor antagonist that showed promising results in preclinical studies, was not proven to be efficient in migraine pre-

vention [179]. The above-mentioned data suggest that therapeutic strategies targeting SP or its receptors might not be adequate for acute or prophylactic migraine treatment.

4.3. Nitric Oxide (NO.)

NO. is a labile gas, produced by three iso-enzymes called NOSs: neuronal (nNOS) inducible NOS (iNOS) and endothelial NOS (eNOS), which have been implicated in migraine pathophysiology [180].

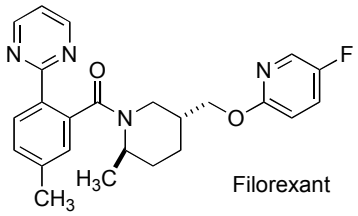

Fig. (5). Synthesis of NO. by NOS.

Indeed, NOS-immunopositive neurons were detected in the TG [131]. Due to the possible vascular side effects via eNOS, the focus has been put on pharmacological studies targeting iNOS or nNOS [181-182]. In clinical studies, no superiority to placebo was noted either as acute or as a prophylactic treatment in migraine [183]. A selective iNOS inhibitor and 5-$HT_{1B/1D}$ receptor agonist has also been assessed, revealing no clinical efficacy. The studies concluded that any future therapeutic approach related to NO. synthesis should be handled with dubitation [168].

4.4. Orexin

The orexin (hypocretin) system is a family of hypothalamic neuropeptides [184] playing a key role in the regulation of sleep and wakefulness [185]. Recent findings have supported the role of orexins in nociception and in migraine as well, as in preclinical studies, orexin receptor antagonists were able to diminish TNC activation following electrical stimulation of dural blood vessels in rat [186]. In phase 2 clinical study, the efficacy of a dual orexin receptor antagonist (MK-6096, filorexant) was tested as prophylactic treatment. This study did not show any evidence supporting the efficacy of filorexant as it was not superior to placebo. Adverse events (including fatigue and somnolence) were more common for filorexant treatment than in placebo. It can be presumed that the unfavorable pharmacological profile of the drug (*i.e.,* rapid T_{max} and short half-life) might be attributable for the negative results [187]. To our knowledge, no clinical trials are ongoing in relation to orexin or its receptors.

CONCLUSION

Taken together, we conclude that currently available clinical and preclinical data provide promising therapeutic targets and tools for future migraine therapies. It is unquestionable that migraine has a high impact on individual and public health. Besides the well-established role of the trigeminovascular system in migraine pathogenesis, the involvement of other brain centers and phenomena such as CSD or neurogenic inflammation have become more and more established. All these demonstrate that much is yet to be unveiled to sufficiently understand the mechanisms regarding the generation of a migraine attack. Except for triptans, all other groups of drugs currently used in the daily practice are not migraine-specific. As CGRP has proven to be a key mediator in migraine, it has become the most promising target for new therapeutic approaches. After the disappointing side effects of telcagepant, the monoclonal antibodies against CGRP can bring a revolution in the preventive treatment of migraine. We hope that the high production costs of these antibodies will not limit their everyday use in the clinical practice. Preliminary data of several phase 3 studies presented on the IHC 2017 are extremely promising.

The selective targeting of the 5-HT_{1F} receptor might overcome the cardiovascular side effects associated with triptans, making lasmiditan a highly promising drug in the future in migraine attack therapy. Glu-related treatments also seem to be effective in acute and preventive treatments of migraine. However, it should be taken into consideration that Glu is ubiquitous in the CNS; therefore possible CNS-related

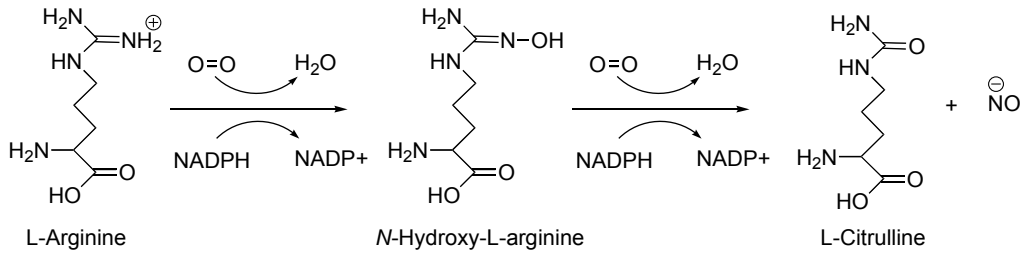

Fig. (6). Chemical structure of Filorexant.

side effects might limit the use of these medications in the daily practice.

It is still a question of debate whether a peripheral site of action per se is sufficient for migraine treatment or an effective substance will need to cross the BBB as well. We assume that the peripheral site of action (predominantly on the TG) might be effective for migraine prevention. To prevent central sensitization, penetration through the BBB is, however, indispensable. The antagonism of PACAP-mediated effects and the KYNA-mediated anti-glutamatergic mechanisms might be promising therapeutic approaches, as suggested by preclinical animal studies. Future research should focus on elucidating the pharmacodynamics of PAC1 antagonists and KYNA analogues. The limitations of preclinical studies need to be emphasized, however, as a number of molecules previously considered effective in animal models were not able to show efficacy in phase 2 clinical trials.

All these support the need of further studies both at the clinical and pre-clinical levels in order to shed light on the ethiopathology of migraine, opening novel lines of therapeutic strategies in this highly disabling neurological condition.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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