

MIGRAINE, A GRAVE FORM OF HEADACHE: A REVIEW ON CURRENT AND PERSPECTIVE RESEARCH

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Abstract

Calcitonin Gene-Related Peptide (CGRP) receptor antagonists and triptans are the lime-lighted targets for migraine treatment for the past two decades. However the hypothetical theories of migraine occurrence (including the reason behind initiation) as well as the complex nature of protein and unclear mechanism of the small molecule drug interaction on the receptors, still exists till date making it a challenging task for scientists to move forward in migraine research. Several pharmaceutical companies and research laboratories worked on anti-migraine drugs and even found out some efficacious, selective and potent drugs in the recent years but failed in the later stages of clinical trials due to different reasons. Hence during the course of this article we shall cover the recent advances, breakthroughs and perspectives in migraine therapy.

Rezumat

Antagoniștii receptorilor CGRP și triptanii au fost țintele principale pentru tratarea migrenelor în ultimii 20 de ani. Oricum, teoriile ipotetice privind apariția migrenelor, precum și natura practică complexă și mecanismul neelucidat al interacțiilor dintre medicamentele cu moleculă mică și receptori, încă îi mai preocupă pe oamenii de știință, reprezentând o provocare pentru continuarea cercetărilor în ceea ce privește migrenele. Câteva companii farmaceutice și laboratoare de cercetare au studiat medicamente antimigrenoase și în ultimii ani au descoperit câteva medicamente, eficiente, selective și potente, dar care nu au reușit să treacă etapa de studiu clinic din diferite motive. În acest context, acest articol se referă la progresele recente, inovațiile și perspectivele terapiei antimigrenoase.

Keywords: Headache, Migraine, Calcitonin Gene-Related Peptide (CGRP), Triptans

Introduction

Headache, one of the foremost neurological disabilities often due to the social and personal burdens is considered as the broad class of different pain forms in the head. It can be classified as [1, 2]:

Primary headaches

Migraine: A persistent headache which affects at an age of 35 to 45 years and stays throughout the patient's life time. It is characterised as pulsating, one sided, intense and occurs due to physical activities.

Tension-type headache (TTH): A stress induced pain, mostly initiating in teenage and affecting 3:2 of female to male subjects. Symptoms include pressure along with tightness in and around frontal part of head and neck.

Cluster headache(CH): A rare form of headache occurring around the age of 20, affecting less than 1 person out of 1000 with a ratio of 1:6 of female to male subjects. Symptoms are severe ache and redness around eyes along with rhinorrhoea.

Secondary headaches

Medication-overuse headache: An induced and persistent, repressive pain due to over use of drugs

against headaches. 5 out of 100 people are affected and is characterised by severe pain especially prominent during awakening.

Altogether, it has been projected that incidents among the adult subjects with headache disorder is 47% among whom 50-75% had headache in the last year which includes 10% with the most predominant and severe forms of headache i.e. migraine [3]. Hence in this review, we mainly cover the past, current as well as future research on migraine along with other aspects of the syndrome.

Migraine

Migraine is a complex vasodilative and incapacitating disorder occurring in almost 15% of the adults throughout the world among whom the female population is affected majorly. It is a periodic affliction characterised as one-sided, pulsating headache associated with photophobia and phonophobia [4]. Typical migraine attack ranges from 1.5 times a month and reaches its toll around an age of 40 years during patient's lifetime [5].

Key facts and figures

≈ 15% of world population suffers from migraine, among which 70% are women. Migraine is a syndrome with a group of symptoms among which, all of them or some of them are shown during one migraine attack. A study among 4000 migraine patients has shown symptoms as follows [6].

Table I
Symptoms in migraine patients

Symptom	Percentage (%)
Pulsating ache	85
Photophobia	80
Phonophobia	76
Gastric related disturbances	73
One-sided pain	59
Visual disturbances	44
Aura	36

50% of the migraine episodes in patients remain un-investigated and not properly treated, half of the subjects remaining un-consulted by the doctor [7]. Migraine is ranked amongst top 20 disabilities throughout the world [8]. In United Kingdom, there are 0.19 million migraine flare-ups each day [9]. Depression is 3 times more often in migraine patients compared to the healthy volunteers. Most

notably, migraine research is the least funded neurobiological disorder when equated with its financial impact on population [10].

Pathophysiology of migraine

The initiation of migraine even after years of research is still unclear. But many hypothetical theories are proposed by different scientists making it a difficult target to work on. One of the main theories which have an adequate theoretical basis is Cortical Spreading Depression (CSD) [11]. CSD onsets as a wave of electrical signal in the cerebral cortex. The key event in unveiling and dissemination of CSD can be related to drastic decrease of neuronal membrane resistance in association with a series of events like extracellular increase of neurotransmitters and potassium (K^+) ions and intracellular decrease of sodium (Na^+) and calcium (Ca^{++}) ions [12]. The modulation of CSD threshold is influenced by several factors like environment, genetic makeup, age, hormones etc. However recent preclinical and clinical investigations showed a clear coherence of migraine with Calcitonin Gene-Related Peptide (CGRP), a potent vasodilator. Hence, most research groups working on migraine shifted their focus onto CGRP in the recent years (Figure 1).

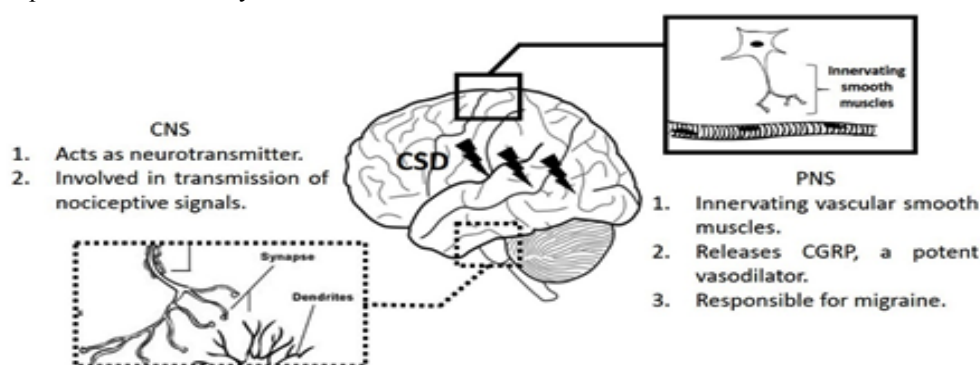


Figure 1.
Distribution and implications of CGRP receptor [15]

Calcitonin Gene Related Peptide

Calcitonin Gene-Related peptide, a 37 amino acid neuropeptide which is involved in several physiological processes came into the lime-light after extensive studies on migraine have shown some interesting facts [13].

Among the migraine patients, the brain plasma showed abnormal increases in CGRP concentration during the attack which inferred the involvement of CGRP in migraine events [14]. This observation has shifted the whole migraine research onto CGRP and its receptor antagonists.

There has been some extensive studies on the distribution of CGRP receptors in recent times stating that they are widely distributed in central

and peripheral nervous system [15]. In central nervous system (CNS), it acts as a neurotransmitter. In peripheral nervous system (PNS) its action has been exploited for its importance in the dilation of smooth muscles which results not only in migraine but also in some neglected visceral disorders like Irritable Bowel Syndrome (IBS) and Crohn's disease.

Therefore, current migraine therapy rationale is based on its mechanism of dilation of cranial blood vessels.

CGRP receptor antagonism

CGRP receptor belongs to the class B of G-protein coupled receptors. It is a heterodimeric protein with

an association between Calcitonin-receptor Like Receptor (CLR) and Receptor Activity Modifying Protein-1 (RAMP-1) [16]. The orthosteric activation of the receptor by the natural ligand CGRP results in a cascade of reactions like activation of Adenylate cyclase enzyme by the G-protein, conversion of Adenosine Triphosphate (ATP) to cyclic Adenosine Monophosphate (cAMP) by the activated adenylate cyclase, activation of Protein Kinase A (PKA) enzyme by

cAMP, phosphorylation of ionic channels by the PKA resulting in opening of ionic channels and consequently an intracellular increase of K^+ and Ca^{++} . Thus these alterations result in hyperpolarisation or vasodilatation [17, 18]. In the case of migraine, due to the vasodilatation or distension of the cranial blood vessels and resistance and limitation from the skull bone results in the pulsating and severe pain in head (Figure 2).

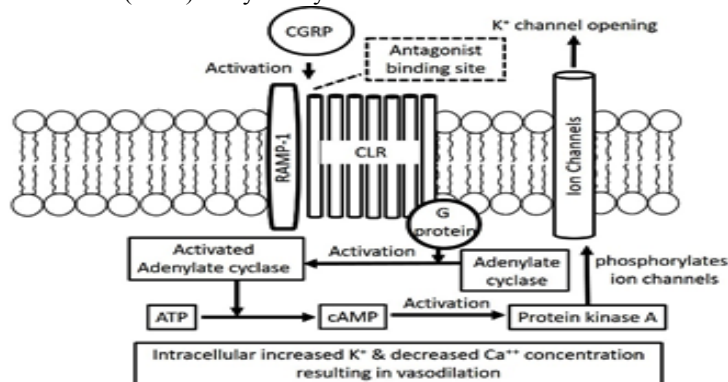


Figure 2.

Molecular cascade events of CGRP receptor activation [19]

In order to counteract this vasodilatation, the binding site of natural ligand is masked using antagonists [19] and the cascade of reactions can be turned off resulting in no vasodilatation step.

Discovery of peptide antagonists for CGRP receptor

CGRP receptor was first antagonised by CGRP₈₋₃₇, a peptide chain of 30 amino acids which was discovered from the intertwining of the natural ligand i.e. CGRP (Figure 3) [17].

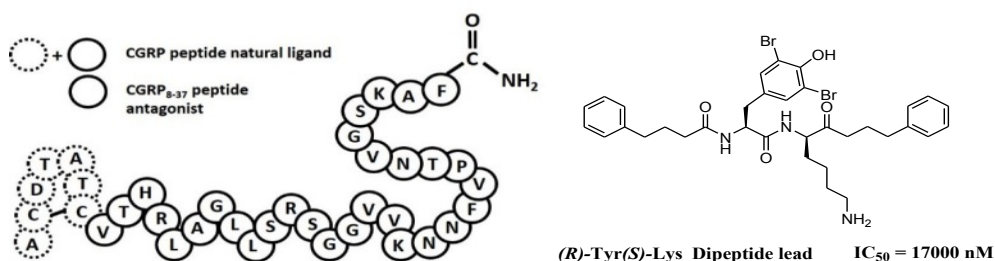


Figure 3.

Peptide antagonists for CGRP receptor [17]

Further research at Boehringer Ingelheim has developed some small peptides derived from the C terminus of the natural ligand [20]. Later on by High Throughput Screening, a (R) Tyr (S) Lys peptide was identified as a lead. A series of

modulations like rigidification of C and N terminus, bio-isosteric replacement keeping the peptide pharmacophore untouched resulted in the first potent CGRP receptor antagonist called BIBN4096 (Olcegepant®) (Figure 4).

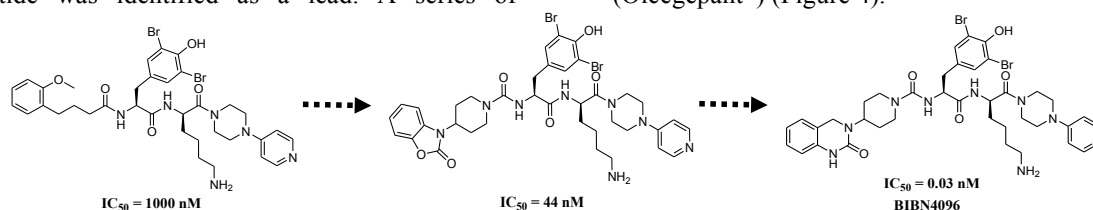


Figure 4.

Sequence of modulations resulting in BIBN4096 [21]

Olcegepant[®] discriminates the rodent and primate CGRP receptors [21]. It has more affinity towards primate receptor with $K_i = 0.014$ nM compared with that of rodent receptor showing $K_i = 3.4$ nM. This is due to the replacement of Tryptophan with Lysine in the 74th position of the receptor in rodent species implying the importance of tryptophan interaction to have potency for small molecules. Even though BIBN4096 is a potent and selective antagonist, the peptidic nature of the molecule has

limited its use due to its poor lipophilicity.

Non peptide CGRP antagonists

MK0974 called Telcagepant[®] is an orally active, potent antagonist developed by Merck & Co. Being a non-peptide, it is more lipophilic with equal potency to BIBN4096 hence advantageous over the latter [22]. Like BIBN4096, it is 1500 folds more selective towards primate CGRP receptor (Figure 5).

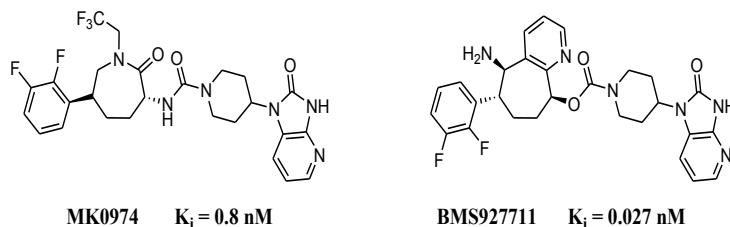


Figure 5.

Non peptide antagonists [22]

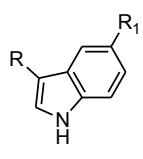
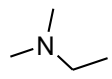
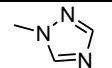
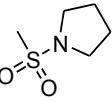
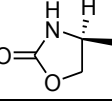
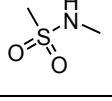
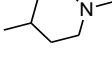
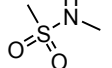
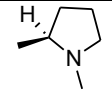
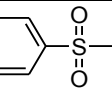
MK0974 was eliminated from its phase III clinical trials as there were cases showing increased serum transaminases, which inclines to hepatotoxicity [23]. BMS927711 by Bristol Myers Squibb is another orally active, potent and selective agent with $K_i = 0.027$ nM, which has recently finished the 2nd of the 3 tests for the approval into the market [24]. Adding to this list, some more non peptide antagonists are currently in their preclinical evaluation [25].

5-HT_{1B/1D} receptor antagonists for migraine therapy; the triptans

The triptans class of drugs are efficacious, potent and mostly used drugs for migraine therapy even at present [26]. The name 'Triptans' indicates their core chemical moiety i.e. tryptamine. All the class of triptans have 5-hydroxy tryptamine as their core moiety. Some triptans are as follows Table II characteristic from.

Table II

Structure and activity of triptans in clinical stage

Name	Core moiety	R	R ₁	Dose (mg)	I	S	C	T	
Rizatriptan				5	=	=	=	=	
				10	+	+	++	=	
Almotriptan				12.5	=	+	+	++	
Zolmitriptan				2.5	=	=	=	=	
				5	=	=	=	=	
Sumatriptan				25	-	=/-	-	+	
				50	=	=	=/-	=	
Naratriptan					2.5	-	-	-	++
Eletriptan					20	-	-	-	=
					40	=/+	=/+	=	=
				80	++	+	=	-	

(I = Initial 2 h relief, S = Sustained pain-free, C = Consistency, T = Tolerability)

(= indicates equal, - indicates less and + indicates more activity when compared with sumatriptan 100mg, N° of subjects - 24089) [27]

Complications of triptans

Alongside its efficacy, triptans have side effects like myocardial infarction, hypertension, tachycardia, angina pectoris, renal and hepatic failures, serious allergic reactions, dry mouth, gastro and heart related problems etc. [28]. Increased doses of sumatriptan result in sulphaemoglobinaemia, a reversible state where blood turns into greenish-black due to the co-ordination of sulphur onto the haemoglobin moiety [29]. A life threatening medical condition called 'serotonin syndrome' is resulted due to drug-drug interaction of triptans with either mono amino oxidase class of anti-depressant drugs or serotonergic drugs [30].

Antibodies and biologics in contemporary migraine market

LB101 (previously RN307), a monoclonal antibody which is used for periodic and long term migraine is now in phase IIb clinical trial. Teva pharmaceuticals acquired it for \$825 million from Labrys Biologics [31]. Zecuity® by NuPathe Inc, an advanced transdermal patch loaded with sumatriptan delivers a dose of 6.5mg over a period of four hours and demonstrated to be effective for migraine. Allergan's Botox® usage is continued as a preventive treatment for chronic migraine. Another monoclonal antibody LY2951742 developed by Arteaus Biotech is also used as a preventive medication. It has recently finished the phase II trials sponsored by Eli Lilly and showed significant efficacy and tolerability [32]. ALD403 by Alder Biopharmaceuticals finished phase II clinical trials and showed radical migraine states improvement (75%) [33].

Conclusions

Triptans class of drugs continued to be the best class of small molecules used for migraine therapy, even though it has side effects on patients with heart related problems. Recent efforts on development of small molecule antagonists of CGRP receptor have showed an unmatched treatment with least side effects. Hence, further studies on CGRP receptor antagonists ranging from small molecules to antibodies and biologics are currently competing in the field of migraine research implying that a true answer for the migraine treatment can be achieved swiftly in less than a decade in the future.

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