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CGRP receptor antagonists: A new frontier of anti-migraine medications

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Abstract

Migraine is a chronic pain condition that affects 12% of the population. Currently, the most effective treatments are the triptans, but they are limited in their efficacy and have potentially deleterious cardiovascular complications. Based on basic science studies over the past decade, a new generation of anti-migraine drugs is now being developed. At the forefront of these studies is a new calcitonin gene-related peptide (CGRP) receptor antagonist that is as effective as triptans in the acute treatment of migraines, without the cardiovascular effects. This review will address the likely mechanisms and therapeutic potential of CGRP receptor antagonists.

Introduction

Migraine is a debilitating condition that affects 12% of the general population at least once a year [1]. It is a chronic disease, with episodic attacks of variable frequency that disrupt normal daily activities and has serious economic repercussions [2].

Migraine attacks are defined as headaches lasting 4 to 72 hours with at least two of the following symptoms: (1) pulsating quality, (2) unilateral location, (3) moderate or severe intensity, (4) aggravation by routine physical activity. In addition, the headache is accompanied by at least one of the following associated symptoms: (1) nausea and/or vomiting or (2) photophobia and phonophobia [3]. In 20-30% of the migraineurs, the headache is preceded or accompanied by focal neurologic phenomena called aura. The aura can be visual, sensory or motor and may involve language or brain stem disturbances [4].

What causes a migraine is still unclear. Many different triggers have been described, from hormonal variations during the normal menstrual cycle to different types of food. The variability and complexity of these triggers has complicated studies on the initial trigger of migraine. The two prevailing theories involve release of biogenic amines from brainstem nuclei [5] and release of compounds during the wave of cortical spreading depression [6]. It seems likely that both mechanisms will play a role in migraine. A common theme of both mechanisms

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is the generally accepted role of the trigeminal ganglion in the painful phase of migraine. The major neuropeptide released at both the central and peripheral terminals of the trigeminal is calcitonin gene-related peptide (CGRP). Over the past decade, CGRP has been implicated as a central player in the painful phase and possibly even the genesis of migraine.

Migraine and CGRP

Migraine is now generally accepted to be a neurovascular disorder in which the dilation of blood vessels and the pain are triggered by neural signals [7-9]. A central component is the trigeminovascular system, which includes the meningeal vasculature and sensory innervations from the trigeminal ganglion. These innervations from the trigeminal ganglion help control cerebral blood flow and provide nearly all of the pain sensitive innervations [10-12]. The trigeminal ganglion is also the major source of CGRP innervation of craniofacial structures and the cerebrovasculature [10,12]. The activation of trigeminovascular afferents in the meninges and at the major vessels leads to release of CGRP and other neuropeptides that cause vasodilation and neurogenic inflammation. Importantly, CGRP is also released at the efferent terminals in the brainstem, where it contributes to nociception [13,14].

The neurovascular model is consistent with clinical evidence that CGRP levels are elevated during migraine and reduced by triptan antimigraine drugs [7,15,16], although the elevation has recently been questioned [17]. A causal role for CGRP in migraine has been revealed by induction of migraine-like headaches following injection of CGRP [18]. Moreover, the change in plasma CGRP levels during migraine attacks significantly correlates with the headache intensity [19]. The triptans are the current drugs of choice for acute migraine treatment. Triptans are 5-HT_{1B/D/F} receptor agonists that attenuate migraine in many patients. Functional 5-HT_{1B/D/F} receptors have been found on perivascular trigeminal nerve terminals and the trigeminal nucleus caudalis in the brainstem [20-23]. Consistent with the multiple locations of the 5-HT₁ receptors, triptans can inhibit vasodilation of intracranial vessels and inhibit CGRP release to block neurogenic inflammation and central transmission of nociceptive stimuli from trigeminal nerves [24].

However, about one-third of patients do not respond to triptans [25]. Whether CGRP levels are altered in these patients has not been addressed. In addition, there is a high recurrence rate of the headache even after taking the drug [26]. A major concern is that triptans can cause severe vasoconstriction of coronary arteries [27]. Because of this, triptans are contraindicated in patients with established cardiovascular disease, and they should be used cautiously in patients with cardiovascular risk factors [25].

Importantly, intravenous infusion of CGRP in migraineurs produces migraine-like headaches [18]. The ability of CGRP to trigger a delayed severe headache, including some of the non-headache symptoms, strongly suggests that CGRP plays a causal role in migraine. In addition, CGRP infusion in non-migraineurs caused a mild headache that was prevented by a CGRP receptor antagonist [28]. The effectiveness of this antagonist was a harbinger of its potential as an anti-migraine drug.

CGRP antagonist as migraine treatment

A recent approach to treat migraines is to reduce CGRP activity by targeting CGRP receptors. The CGRP receptor is composed of 3 subunits: a 7-transmembrane protein called calcitonin-like receptor (CLR), a single transmembrane protein that determines ligand specificity called receptor activity modifying protein 1 (RAMP1) and an intracellular protein called receptor component protein (RCP). The CGRP receptor is mainly coupled to the G α s signaling pathway leading to increased intracellular cAMP and activated protein kinase A (PKA) (see Fig. 1) [29].

There are multiple sites of CGRP action that may be relevant during migraine [30]. First, CGRP receptors are located on the cerebrovasculature smooth muscle where they cause vessel relaxation [18]. Second, CGRP receptors are present on dural mast cells from which CGRP has been shown to release pro-inflammatory cytokines and inflammatory agents during neurogenic inflammation [31]. Third, there are CGRP receptors on the trigeminal ganglia neurons [32-34] and postsynaptic CGRP receptors on second-order sensory neurons within trigeminal nuclei in the caudal brainstem that transfer the pain sensation [35].

First approach: peptide CGRP antagonists

The first CGRP receptor antagonists developed were C-terminal truncated CGRP fragments [36]. The CGRP₈₋₃₇ peptide includes all but the 7 first amino acids of CGRP. CGRP₈₋₃₇ works as competitive antagonist, blocking the binding of full length CGRP. Although CGRP₈₋₃₇ has been shown to inhibit neurogenic vasodilation induced by trigeminal ganglion nerve stimulation [24], it has been proved ineffective clinically due to its low potency and short half-life [36]. Another C-terminal truncated CGRP fragment with higher affinity for CGRP receptor has been developed, CGRP₂₇₋₃₇, but it has the same limitations as CGRP₈₋₃₇ [37].

An approach that works: non-peptide CGRP antagonist

Three non-peptidic CGRP receptor antagonist has been recently developed: BIBN4096BS or olcegepant [38], Compound 1 [39] and SB-(+)-273779 [40]. Both Compound 1 and SB-(+)-273779 inhibited CGRP binding to SK-N-MC cells (human neuroblastoma cell line) and reduced CGRP-induced increase in cAMP [14,40]. In addition, SB-(+)-273779 antagonized CGRP-induced vasodilation and decreased blood pressure in animal models [40]. The specific affinities of the three antagonists seem to depend on its interaction with the RAMP1 subunit of the receptor [41]. BIBN4096BS shows a >1000-fold higher affinity for the receptor than Compound 1 and SB-(+)-273779 [38].

The anti-migraine capacity of BIBN4096BS was tested in animal models showing that BIBN4096BS clearly attenuated the vasodilation induced by trigeminal stimulation [38] and capsaicin-induced carotid vasodilator responses [42]. Besides these effects on the vessel CGRP receptors blocking vasodilation, BIBN4096BS has been shown to lower the activity of neurons of the rat spinal trigeminal nuclei [43]. This central activity blocking the receptors on the secondary neurons of the brainstem could be key for blocking the transmission of the pain information during the migraine. Importantly, BIBN4096BS had no effect on baseline systemic and regional hemodynamics in rat models, suggesting cardiovascular safety [13].

Recently, a phase II clinical trial has shown its efficacy in the acute treatment of migraine [44]. A total of 126 migraineurs were randomized to receive BIBN4096BS or placebo. The patients treated with BIBN4096BS had both decreased headache and improvements in the associated symptoms of nausea, photophobia, phonophobia, and inability to function. The main side effect to the drug was mild paresthesias that occurred in 7% of the subjects, other side effects were nausea, headache, dry mouth and abnormal vision; they were very infrequent (2% each). As mentioned above, BIBN4096BS was also effective at preventing CGRP-induced headache [28]. Importantly, the drug does not appear to affect the baseline cerebral or systemic hemodynamics [45] or any adverse cardiovascular effects when used as a migraine treatment [44,28].

This lack of cardiovascular effect is the major advantage of BIBN4096BS over triptans since both anti-migraine drugs have a response rate of around 60% of patients in two hours. It is yet to be determined if patients that do not benefit from triptans would respond to BIBN4096BS. Even if this were not the case, BIBN4096BS would be a suitable treatment to patients with cardiovascular diseases that cannot be treated with triptans.

Alternatives to intravenous administration: Benzodiazepinones

The major challenge for acceptance as BIBN4096BS as an anti-migraine treatment is its intravenous administration [30]. Searching for a more suitable administered formulation Williams and co-workers [46] identified 10 different benzodiazepinones as CGRP antagonist with different affinities for the human CGRP receptor. Among these, benzodiazepinone piperindinyldihydroquinazoline 7 (Compound 7) had the higher affinity. It was lower than the affinity of BIBN4096BS but higher than Compound 1 in vitro. Compound 7 anti-migraine properties have yet to be studied although it has been shown to be orally bioavailable in rats [46].

Conclusions

Based both on experimental and clinical data, CGRP is believed to play a central role in migraine. The heterogeneous etiology of migraine has led to the strategy of regulating CGRP neurotransmission. While the currently used triptans inhibit CGRP release and decrease pain sensation, the triptans have limitations due to their potential cardiovascular complications. A new frontier of migraine therapy has been opened up by the recent development of the CGRP receptor antagonist BIBN4096BS, which has anti-migraine effects without apparent cardiovascular effects. The efficacy of BIBN4096BS has raised several fundamental questions about the sites of CGRP action in migraine. We propose that CGRP acts at both peripheral and central sites of the trigeminovascular system contribute to migraine. Another key aspect for future treatment of migraine will be to understand the basis of the heterogeneity of the syndrome. Are there differences in response to treatment, triggers and symptoms that are due to individual differences in pain thresholds and CGRP expression and action or other hormonal variations? Future studies on the mechanisms controlling CGRP synthesis, release and receptor action, and the use of different formulations of CGRP antagonists will continue to provide insight to the pathology of migraine.

Related links

International Headache Society www.i-h-s.org

American Headache Society www.americanheadachesociety.org

The National Migraine Association www.migraines.org

MedlinePlus: Migraine www.nlm.nih.gov/medlineplus/migraine.html

www.drugdevelopment-technology.com/projects/olcegepant/

Related articles

Arulmani, U. et al. (2004) Calcitonin gene-related peptide and its role in migraine pathophysiology. *Eur. J. Pharmacol.* 500(1-3), 315-330

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Figure 1.

Calcitonin gene-related peptide receptor binding. Calcitonin gene-related peptide (CGRP) receptor is composed of 3 subunits: one main 7-transmembrane protein called calcitonin-like receptor (CLR) and two modifying subunits, receptor activity modifying protein 1 (RAMP1) and receptor component protein (RCP). **(a)** When CGRP binds its receptor, it activates adenylate cyclase to increase intracellular cAMP. **(b)** When CGRP antagonist binds to the CGRP receptor, CGRP is not able to bind the receptor and there is no increase of intracellular cAMP and the cellular actions of CGRP are blocked. Abbreviations: AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; CLR, calcitonin-like receptor; Gα, G protein α; RAMP1, receptor activity modifying protein type 1; RCP, receptor component protein.

Table 1
Comparison of the different migraine treatments affecting CGRP physiology

	Triptans	Peptidergic antagonist	Non-peptidergic antagonist	
			BIBN4096BS	Compound 7
Pros	Preferred drug nowadays 60% patients pain free in 2h	Specific CGRP antagonist. High affinity	60% patients pain free in 2h No CV [*] secondary effects	Structurally similar to BIBN4096BS. Should work in a similar way. Orally available
Cons	33% of patients don't respond Not indicated in CVD [*] patients	Low potency and short half life	i.v. [*] administration	Still has not been try in animal models
Developments		Ineffective clinically	Phase II Clinical	Early preclinical stages
Who is working on this strategy?			Boehringer-Ingelheim	Merk&Co.
References	[24-27]	[36,37]	[28,44,45]	[46]

^{*} Abbreviations: CV, cardiovascular; i.v, intravenous; CVD, cardiovascular disease.