Drugs Against Calcitonin Gene-Related Peptide and its Receptor Used in the Treatment of Migraine: What are the New Progresses?

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ABSTRACT

Migraine is a chronic headache disorder that its exact pathomechanism is not very well known but research in the last two decades indicates that it might be a brain disorder, a dismodulation of sensory processing of the brainstem responsible for regulation of vascular tone and the pain. Several neurotransmitters and neuromodulators including neuropeptides have been implicated in the pathomechanism of migraine, among them, Calcitonin gene-related peptide (CGRP) has been the focus of many studies in recent years. Increased CGRP level (perhaps due to release from peripheral and central sensory nerve endings) has been detected in the blood of migraine patients and many basic and clinical investigators in recent years have been trying to block the CGRP receptor by means of newly developed CGRP-receptor antagonist drugs or inhibit its activity by even newer compounds, the monoclonal Antibodies (mAbs) against CGRP or its receptor. These latter ones are still in clinical trials but have had promising results so far in alleviating the pain of migraine patients. This article will briefly review and discuss the role of CGRP and its receptor in migraine and some of the other biological activities of CGRP, the CGRP receptor antagonist drugs and the new progresses in mAbs against CGRP or its receptor.

KEYWORDS: Migraine; Calcitonin gene-related peptide.

ABBREVIATIONS: CGRP: Calcitonin gene-related peptide; mAbs: monoclonal Antibodies; TG: Trigeminal Ganglion; NSAIDs: Non-steroid anti-inflammatory drugs; CLR: Calcitonin receptor-like receptor; RAMP1: Receptor activity-modifying protein 1; RCP: Receptor Component Protein; TNF: Tumor Necrosis Factor; IL-10: Interleukin-10; TLR4: Toll-like receptor 4; eNOS: endothelial Nitric Oxide Synthase; ASD: Autism Spectrum Disorders; RNA: Ribonucleic acid; BBB: Blood Brain Barrier.

INTRODUCTION

Migraine is believed to be a brain disorder, a deficiency of sensory modulation, and probably a system failure of normal sensory processing of the brainstem that regulates the vascular tone and the pain in migraine. Although the aura phase of migraine is believed to be due to cortical spreading depression, a similar mechanism of neuronal excitation is believed to be the trigger for migraine while the headache phase of migraine seems to involve the trigemino-vascular system consisting of mainly trigeminal nerve and meningeal vessels.

Observations of Dr. Goadsby and several investigators using imaging studies suggest that the trigger phase of migraine is initiated by neuronal hyperexcitability and activation of the brainstem, hypothalamus, and the brain, and that activation is often unaffected even after relief of the headache by antimigraine drugs.
A major part of the dura mater specially the supratentorial part of dura is innervated by the trigeminal nerve, mainly the ophthalmic branch. The Trigeminal Ganglionic (TG) neurons contain several neurotransmitters and neuromodulators among them glutamic acid and various neuropeptides including the calcitonin gene-related peptide. Several neuropeptides coexist together in TG sensory neurons and may be released at the first central trigeminal synapses in the brainstem upon stimulation, but clinically, significant CGRP increase has been seen in migraine patients. CGRP administration in human provoked a migraine-like attack in migraine patients and CGRP-antagonists alleviated the headache to a comparable level to other potent anti-migraine drugs such as sumatriptan. Currently, some of the first choice antimigraine drugs include the triptan family drugs that are the serotonin receptor agonists (5-HT1B/D), and the Non-steroid anti-inflammatory drugs (NSAIDs) according to the “European Federation of Neurological Societies (EFNS)”. Please see for a comprehensive review of the triptan family drugs and their receptors, and see for a brief review of several other drugs that are being used for the treatment of migraine including their actions, effects and side effects.

However, research in the treatment of migraine is one of the active fields of the neurological research and several studies in recent years focused on new and alternative treatment strategies including antagonizing CGRP receptors and/or blocking the CGRP activity by mAbs against CGRP and/or its receptor.

Calcitonin gene-related peptide consists of 37 amino acid detected by alternative processing of Ribonucleic acid (RNA) transcripts from the calcitonin gene which result in the production of distinct messenger RNA (mRNAs) that encodes the hormone calcitonin.

There are two forms of CGRP in humans: the α-CGRP and the β-CGRP that are derived from different genes that differ in 3 amino acids but show similar functions. The α-CGRP is expressed in sensory neurons including the trigeminal ganglion and is the relevant one in migraine pathophysiology while the β-CGRP is expressed in the enteric nervous system and in hypophysiosis and its role in migraine is not known.

There is a wide anatomical distribution of CGRP in the body including the central and peripheral nervous system and is involved in many functions including nociception, glucose uptake, and stimulation of glycolysis in the skeletal muscles. CGRP is a potent vasodilator in human and rat and may mediate hyperemia in some pathological conditions.

The headache phase of migraine is believed to be caused by vasodilatation of cranial vessels activating the trigeminal and other sensory nerves, although migraine has been reported without the initial dilatation of the middle cerebral artery and even during cerebral hypoperfusion.

CGRP Receptor and its Localization in the Nervous System

CGRP receptor has an unusual structure and consists of a hetero-oligomeric complex with a transmembrane Gs protein-coupled receptor, the “Calcitonin receptor-like receptor (CLR)” and an accessory protein known as the “Receptor activity-modifying protein 1 (RAMP1)” which is necessary to transport CLR to the plasma membrane. Both the CLR and RAMP1 subunits have extracellular domains that interact with one another and together form a complex for the peptide-binding site. The extracellular domain of RAMP1 is very important for the binding of CGRP-receptor antagonist molecules to the CGRP receptors and function of RAMP1 is crucial for the activity of CGRP receptor in the trigeminal ganglion. Another related structure of the CGRP receptor is the Receptor Component Protein (RCP) which is crucial for signaling pathway and determines the G-protein to which the receptor should be coupled with.

The CLR acts as a receptor for either CGRP or adrenomedullin, depending on which members of RAMPs are expressed. RAMP1 is a CGRP receptor at the cell surface and acts as a mature glycoprotein as well. RAMP2-transported receptors are adrenomedullin receptors and are core-glycosylated molecules.

Although originally two CGRP receptors (1 and 2) were recognized the nomenclature changed later and the “CGRP(1)” receptor is now known as the “CGRP” receptor.

Various signaling molecules and second messengers are involved following the CGRP receptor activation. These include the CGRP activation of ATP-sensitive K+ channels or large-conductance Ca2+-activated K+ channels with a subsequent increase of intracellular cAMP leading to vasodilatation and headache. Nitric oxide activation of CGRP release in trigeminal ganglion neuronal cell culture however involves extracellular calcium and T-type calcium channels.

CGRP receptor (both CLR/RAMP1 components) mRNA and protein are expressed in several regions of the CNS including the spinal cord and spinal trigeminal nucleus, area postrema, pineal gland, parts of hypothalamus, periaqueductal gray matter, pontine raphe nuclei and the gracile nucleus although the RAMP1 mRNA was also detected in several regions of the brainstem and that CGRP receptor was found in areas that were not supported by BBB.

CGRP receptor is also expressed in the cerebellum. Localization of the CGRP receptor in the tigeminovascular system seems to be on the central trigeminal nerve endings, dural blood vessels and mast cells, and trigeminal ganglion as well as dorsal horn secondary neurons. Please see for a comprehensive review of the CGRP receptor sites. CNS glial cells such as astrocytes and microglial cell and Schwann cells also express CGRP receptors as well.
CGRP Receptor Antagonists in the Treatment of Migraine

One of the important properties of CGRP-antagonist drugs such as BIBN4096BS is that it prevents the CGRP-mediated vasodilation or activation of trigeminovascular afferents without the vasoconstrictor activities which is an advantage in patients with coronary heart disease or in patients with second rebound attack, see for review.

The discovery of CGRP-antagonist drugs the “gepant” family, in the last decade was a breakthrough in migraine treatment research due to their lack of vasoconstrictive activity compared to some “triptan” family drugs. One of the first drugs, the BIBN4096BS, also known as olcegepant, prevents the CGRP-mediated vasodilation or activation of trigeminovascular afferents, and presumably inhibits the central CGRP receptors.

Olcegepant is a potent anti-migraine drug that has been examined on human arteries. The BIBN4096BS was shown to block the responses evoked by stimulants such as α-CGRP and capsaicin, or transcranial electrical stimulation of perivascular trigeminal nerve which reduces the increased dural blood flow without changing basal vascular parameters, whereas sumatriptan reduced only the vasodilation induced by electrical stimulation. One important advantage of olcegepant over the triptan family drugs is that it doesn’t constrict the coronary arteries.

Olcegepant has been shown to inhibit CGRP receptor in the trigeminal nucleus suggesting a similar central nervous system mechanism as well in treatment of migraine. Another drug in this class, the MK-0974 (telcagepant) is another effective CGRP receptor antagonist when administered orally for the acute treatment of migraine.

Both olcegepant (iv) in phase I, phase II and telcagepant (oral) in phase III have been used in migraine clinical trials. The efficacy of the CGRP antagonists in the central modulation of pain in the hypothalamus has also been reported by Goadsby and colleagues. A major side effect of these drugs is hepatic toxicity and elevated transaminase levels although the presumably high doses of olcegepant and telcagepant alleviating the migraine symptoms are not so high after all. A newer CGRP antagonist “BI44370TA” was reported to have a lower frequency of adverse effects in its phase II clinical trials. It seems that the CGRP antagonists can act on CGRP receptors however it is uncertain whether they act on peripheral or central sites or both in migraine.

Please see for a comprehensive review on the CGRP and its functions, receptors, and the implication of CGRP-receptor antagonists as a novel approach in the treatment of migraine attacks. A recent report comparing the dose-response curve for the efficacy and adverse effect of several serotonin receptor (5-HT\textsubscript{1D}) agonist drugs such as triptans or Lasmiditan (5-HT\textsubscript{1F} antagonist) and the CGRP-receptor antagonists such as telcagepant, B144370TA, MK-3207, and BMS-927711 indicates that the dose-response curve for efficacy of triptans is flat while their adverse effects increase by increasing the doses. While Lasmiditan and the CGRP-receptor antagonist drugs had also a flat dose-response curve, the efficacy-tolerability profile of the triptans is more favorable than others.

Nevertheless, these newer drugs may have advantage in those patients that are triptan non-responders or with coronary heart disease or in patients with second rebound attack. So far five different CGRP-receptor antagonist drugs with proof of efficacy have been used for the treatment of migraine but were discontinued due to hepatic toxicity and other side effects.

Therefore, search for newer drugs against CGRP did not stop but this time, efforts were on developing antibodies against CGRP and its receptors.

Monoclonal Antibodies against CGRP and its Receptor in the Treatment of Migraine Headaches

Antibodies against viruses have long considered as effective preventive methods in viral infections. Antibodies against biological antigens (in this case, CGRP) can bind proteins and neutralize their effect (block the activity) whether being free in the circulation or membrane-bound and possibly intracellular proteins.

Monoclonal antibodies (mAbs) against CGRP and its receptors are newer drugs that have emerged in recent years. Several investigators have been studying three mAbs against CGRP and its receptors. The ALD 403: a humanized Anti-CGRP mAb that has been positive proof-of-concept in phase 2a with a single i.v. dose of 1000 mg that can be repeated every 3-month. The safety of the drug was assessed at 12 weeks after the infusion; the primary efficacy endpoint was observation of changes in the frequency of migraine days from the baseline to weeks 5-8 among adult patients age 18-55 years who had 9-10 days of headache per
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released results (reported by PRNewswire) of a global phase 2 clinical trial (which was also presented in the 17th congress of the International Headache Society, Valencia, Spain) indicate that this fully human mAb, the AMG 334 seems to have significantly decreased the mean migraine days per month in episodic migraine patients.114,115 These studies are currently ongoing but please see references112,113 for more details of AMG 334 studies that has been released so far.

**Biological Role of CGRP in Homeostasis**

So far we discussed the CGRP being a neurotransmitter/neuromodulator that mediates vasodilation peripherally and acting on its receptor on central neurons but it is important to discuss some other biological roles of CGRP in the body.

In the lung and respiratory airways, in addition to CGRP expression of the sensory nerves innervating the airways, blood vessels and lymphoid tissue,116 CGRP is also localized in specialized epithelial (neuroendocrine) cells in the lungs and is involved in regulation of vascular tone,117 protection of the bronchial tree, the anti-inflammatory responses and tissue repair.118 Ablation of sensory nerve fibers leads to a significant increase in inflammatory responses, and congenital CGRP-knockout mice have increased reperfusion-induced tissue inflammatory activities.119 In the gastrointestinal (GI) tract, stimulation of sensory nerves reduces reperfusion-induced liver injury and stressed-induced gastric mucosal injury in rodents presumably by CGRP-induced increase in the expression of prostacyclin [PGI(2)] and attenuation of inflammatory responses such as tissue Tumor Necrosis Factor (TNF) increase and tissue accumulation of neutrophils.119

CGRP is a negative regulator of innate immune responses by inhibiting the antigen presenting cells such as macrophages and dendritic cells, blocking their capacity to produce proinflammatory cytokines.208,210 This effect of CGRP is mediated by production of Interleukin-10 (IL-10) and IL-10 independent processes that stimulate the expression of the inducible cAMP early repressor (International Confederation of Energy Regulators (ICER)) and inhibition of NF-κB, although in sepsis this effect of CGRP may complicate the situation.211 A central role for intestinal dendritic cells in neuroimmune communication and similar roles for neuropeptides including CGRP in the skin, lung and GI tract has also been proposed.212

The Toll-like receptor 4 (TLR4), a bacterial gram negative receptor, can activate the Vanilloid receptor 1 (transient receptor potential action channel subfamily V member 1, TRPV1) and result in the release of CGRP and its anti-inflammatory effects in the intestine.213

CGRP expressing nerve fibers in the GI tract are involved in pain, GI motility and secretion, defense against irritants, and wound healing of ulceration, presumably acting via TRPV1 receptor.214 The central action of CGRP controls the GI motor function and intestinal motility including the migrating motor complexes.215

CGRP and TRPV1 (and some other neuropeptides and receptors/channels) are also involved in the neural plasticity of almost all parts of GI tract including the liver and pancreas during pathological conditions.126

CGRP release from the mesenteric perivascular nerve fibers increases the induction of Pannexin-1-formed channel opening (hemichannels) which results in reduction of pannexin-1 and endothelial Nitric Oxide Synthase (eNOS) expression, and CGRP blockade increases the eNOS expression significantly.127 These channels are important in the regulation of blood brain barrier as well.

There are evidences that CGRP expressing fibers of trigeminal ganglion innervate the pineal gland in several mammalian species.128 Pineal gland is known to regulate hypothalamus, the command center for the control of autonomic and endocrine activities. Although this might be involved in the autonomic responses of pain following activation of the trigeminovascular system.

There is even a role for CGRP in the neuromuscular transmission. CGRP seems to significantly stimulate the calcium (Ca++) channels at the sarcolemmal reticulum leading to Ca++ release into the cytosol of the skeletal muscle and also stimulate the Ca++ channels at the sarcolemma to a lesser extent.129

CGRP expression increases in injured motor neurons and is believed to activate neuroglial cells such as astrocytes and microglial cells in the CNS which is believed to be responsible for tissue remodeling and repair.12

**DISCUSSION**

Several anti-migraine drugs have been developed in the past three decades. Tremendous efforts by brave scientists, clinicians, drug companies, and patients (for clinical trials) in this field has contributed to the significant achievements so far and this effort continues until various treatment options for migraine are found.

Although CGRP has several important roles in human body, increases in its levels in the blood of migraine patients has been linked with the headache. Therefore, inhibiting its activities by means of CGRP-receptor antagonists and/or monoclonal antibodies against CGRP or its receptor has been a focus of more than a decade of research to find another alternative treatment to alleviate the pain of migraine specially on those who are non-responsive to other drugs and also find a more convenient type of medication that patients could take once a month or so and become pain free.
Anti-CGRP treatment strategy is one of the alternative therapies to a number of drug treatment options currently available for the prophylaxis and treatment of headache in migraine. Currently, the first choice treatment options of migraine include the use of triptan [serotonin (5-HT₁₆)] receptor agonist family drugs and NSAIDs. A number of prophylactic drugs such as the Antiepileptic drugs (AEDs), beta blockers, and Ca²⁺ channel blockers are currently being used to treat migraine. These are in addition to other drugs and non-drug treatment options that are currently available to treat migraine headache. Nevertheless, research in the treatment of migraine is always looking for newer and more convenient, more efficient and more potent drugs or treatment strategies with fewer or no adverse effects.

Although promising, the CGRP-receptor antagonist drugs (the “gepant” family) were discontinued due to their side effects, especially the hepatotoxicity. Several other CGRP receptor antagonists such as MK-3207, BI 44370, BMS-846372 are still in clinical trials, please see⁷⁷ for review. Search for newer anti-CGRP compounds with sufficient efficacy and less or no adverse effects continued in recent years.

It seems that blocking CGRP or its receptor alleviates the headache in migraine patients. A number of studies so far in phase one and phase 2, using mAbs against CGRP or its receptors have shown a decrease in the number of headache days per month while did not have a significant adverse effect although these studies are still ongoing at the moment. One important fact about CGRP mAbs is their half-life (and their clearance from the body) which is in the range of a few weeks. This is very good and convenient for migraine patients since with one injection or so per month they experience much less headache days per month although the clearance time of the mAbs from the body is also extended equally.

If proven effective with minimal or no significant adverse events after completing the clinical trials, mAbs against CGRP or its receptors will be another revolution like the triptan family drugs in the field of migraine treatment and will increase our abilities and options to treat migraine effectively. Some of the adverse events of mAbs against CGRP such as infections and abdominal pain seen in some patients may correspond to decrease or inhibition of biological activities of CGRP or activation of some other compensatory mechanisms. Therefore, long term use and monitoring of the patients would add more knowledge to our current understanding.

Such mAbs will certainly be beneficial in other painful or other conditions if their pathophysiology is similar. The four neuropeptides that were increased in the archived neonatal blood of infants who were later (after couple of years) diagnosed having Autism Spectrum Disorders (ASD) or mental retardation. It is not known why some neuropeptides are increased in ASD, but increased blood serotonin levels has been linked to loss of brain serotonergic terminals via a negative feedback, disrupting the serotonin function leading to a compensatory increase in CGRP level in ASD patients. Although, several genes have been implicated in ASD and environmental factors including GI abnormalities and immune imbalance might play a role in ASD and other psychological health problems.

The role of CGRP increase in ASD children is not very well known but both serotonin and CGRP are involved here as well. Some GI problems including diarrhea and abdominal pain in autistic children are due to various causes but the exact pathomechanism of GI problems in ASD children is not completely understood. It is however possible that anxiety, sensory over-responsivity and GI problems are interrelated phenomena in children with ASD.

Several studies using CGRP knockout mice or other related studies have reported about the various roles of CGRP in pathological conditions in animal studies and results are indicative of some protective and some deleterious effects of CGRP in neuroprotection, immune activation or vascular structure and function. However, mAbs against CGRP in migraine treatment research should tell us more about the long term effect of CGRP inhibition.

Interestingly, inhibiting the TRPV1 receptor or interfering with CGRP activity may improve health and increase age longevity as shown in a recent study in mice and brought the ideas of “die another day” and “a long pain-free life”. Can mAbs against CGRP increase our longevity?

CONFLICTS OF INTEREST

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