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CGRP Receptor Antagonists in the Treatment of Migraine

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Abstract

Based on preclinical and clinical studies, the neuropeptide calcitonin gene-related peptide (CGRP) is proposed to play a central role in the underlying pathology of migraine. CGRP and its receptor are widely expressed in both the peripheral and central nervous system by multiple cell types involved in the regulation of inflammatory and nociceptive responses. Peripheral release of CGRP from trigeminal nerve fibers within the dura and from the cell body of trigeminal ganglion neurons is likely to contribute to peripheral sensitization of trigeminal nociceptors. Similarly, the release of CGRP within the trigeminal nucleus caudalis can facilitate activation of nociceptive second order neurons and glial cells. Thus, CGRP is involved in the development and maintenance of persistent pain, central sensitization, and allodynia, events characteristic of migraine pathology. In contrast, CGRP release within the brain is likely to function in an anti-nociceptive capacity. This review will focus on the development and clinical data on CGRP receptor antagonists as well as discussing their potential roles in migraine therapy via modulation of multiple cell types within the peripheral and central nervous systems.

Keywords

migraine; trigeminal ganglion; RAMP1; sensitization

Migraine is a complex neurovascular disorder that affects 12% of the general population [1–3] and is characterized by intense head pain that can be accompanied with sensitivity to light (photophobia), sound (phonophobia), and nausea. Activation of the trigeminovascular system is believed to be a primary pathway leading to the pain associated with migraine. The trigeminovascular system is comprised of nociceptive nerves from the first or ophthalmic region of trigeminal ganglia, the major vessels responsible for regulating cerebral blood flow, and the smaller vessels in the pain-sensitive covering of the brain, known as the meninges [4]. The trigeminal ganglion consists of psuedounipolar nerve cells, primarily Aδ and C-fibers, that are responsible for transmission of nociceptive information originating from meningeal blood vessels to the caudal brain stem or high cervical cord that leads to headache pain [5–9]. While the mechanism by which a migraine attack is initiated is not well understood, dysfunction in the central nervous system (CNS) leading to release of inflammatory mediators is proposed to cause sensitization and excitation of trigeminal nerves that promote neurogenic inflammation and generation of painful stimuli [10–13]. Activation of trigeminal nociceptors mediates the release of neuropeptides, such as calcitonin gene-related peptide (CGRP), substance P, and neurokinin A, from primary sensory nerve fibers that are involved in pain transmission [14–16].

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1. CGRP and Migraine

Based on theories on migraine pathology, activation of trigeminal ganglion nociceptive neurons and the subsequent release of CGRP, but not substance P or neurokinin A, are implicated in migraine pathology [17, 18]. In humans, CGRP exists in two forms that are termed α-CGRP and β-CGRP, which are derived from separate genes and differ by three amino acids yet exhibit similar biological functions [19–22]. The 37-amino acid neuropeptide α-CGRP, which arises from alternative splicing of the calcitonin-CGRP gene [23], is the main form expressed in trigeminal ganglia neurons [19] and the form most essential to migraine pathology. In contrast, β-CGRP, which is encoded by a different gene that is highly homologous to the calcitonin-CGRP gene, is primarily expressed in enteric nerves and in the pituitary gland [24] and its role, if any, in migraine is not known. Thus, the focus of this review will be on understanding the role of α-CGRP, which will be referred to simply as CGRP, and activation of the CGRP receptor in migraine pathology.

CGRP is widely distributed in the central and peripheral nervous system [22] where it is predominantly expressed in C and Aδ nerve fibers that transmit nociceptive signals to the central nervous system (CNS) [12]. Although a complete understanding of the pathogenesis of migraine is not clear, several lines of evidence in migraineurs support a role of CGRP as a key mediator of migraine pathology. For example, CGRP levels in the cranial circulation as well as in saliva are increased during a migraine attack [25–27]. Further evidence for CGRP having a central role in migraine has been demonstrated by data from studies showing that successful treatment of migraine headache pain with the 5-hydroxytryptamine$_{1B/1D}$ agonist sumatriptan, as well as other triptan drugs, resulted in the normalization of CGRP levels [27, 28]. Finally, compelling proof for a central role of CGRP in migraine was obtained with the demonstration that infusion of human CGRP could provoke a migraine attack in susceptible individuals [29] and intravenous administration of the potent CGRP receptor antagonist olcegepant (BIBN4096BS) could abort acute migraine attacks to a comparable degree as reported for sumatriptan [30].

Based on the cellular expression of CGRP and its receptor, CGRP is thought to contribute to the underlying pathology of migraine at multiple sites within the trigeminovascular system [12, 13]. For example, CGRP released from fibers that are associated with meningeal vessels is thought to mediate vasodilation and mast cell degranulation. Activation of the platelets and mast cell degranulation would lead to the release of pro-inflammatory agents that mediate sensitization of trigeminal nociceptors and may be involved in sustaining the painful phase of migraine [31]. The sterile inflammatory process is thought to cause sensitization of the nerve fibers, thus lowering the pain response threshold to previously innocuous stimuli, such as blood vessel pulsations and head movements [32, 33]. Following trigeminal nerve activation, CGRP would be released from fibers projecting to the trigeminal nucleus caudalis that facilitate excitation of second order neurons and glial cells involved in the initiation and maintenance of persistent pain. In addition, CGRP released from the cell body (soma) of trigeminal neurons is thought to act in an autocrine manner to stimulate its own synthesis as well as function in a paracrine manner to stimulate cytokine production in satellite glial cells [34, 35]. CGRP release from trigeminal ganglion nerve cell bodies would induce further CGRP synthesis as well as stimulate satellite glial cells to release inflammatory cytokines and nitric oxide that would promote peripheral sensitization of trigeminal nociceptors. The involvement of CGRP in peripheral and spinal nociceptive mechanisms is well established [36–42]. Spinal application of CGRP facilitates nociceptive behavior [39, 41, 43] and sensitizes the responses of dorsal horn neurons to innocuous and noxious peripheral stimulation [38, 41, 44]. In addition, blockage of CGRP receptors with the peptide antagonist (CGRP$_{8–37}$) or antiserum resulted in anti-nociception in animal models of inflammatory [40] or central neuropathic pain [45]. Taken together, results from these studies

support an important role of CGRP in the development and maintenance of peripheral sensitization of trigeminal ganglion neurons and central sensitization of second order neurons, which are key pathophysiological events associated with migraine. Given the central role of CGRP in migraine, blocking the physiological effects of CGRP would be a logical therapeutic target.

2. CGRP Receptor

Although historically CGRP receptors have been divided into two classes referred to as CGRP1 and CGRP2, recent data have clarified that the CGRP1 receptor is the only CGRP receptor [46]. Functional CGRP receptors are composed of a G protein-coupled receptor known as the calcitonin-like receptor (CLR), a single transmembrane domain protein called receptor activity modifying protein type 1 (RAMP1), and a receptor component protein (RCP) that defines the G-protein to which the receptor couples [47]. RAMP1 is essential for the formation of functional CGRP receptors since it is responsible for trafficking mature CLR proteins to the surface of the cell membrane as well as defining the relative potency of ligands for the receptor [48]. While structure-function investigations have demonstrated that an 18 amino acid sequence located at the N-terminus of the CLR is important for CGRP docking, it does not appear to be involved in the activation of the mature CGRP receptor [49]. In contrast, binding studies have demonstrated that the first seven N-terminal amino acids are essential for receptor activation [50]. Importantly, while deletion of amino acids 2 and 7 that are involved in the formation of a disulfide bridge does not affect receptor affinity, deletion of these amino acids resulted in a total loss of biological activity of the CGRP receptor [51]. Given these findings, it is not too surprising that the first CGRP receptor antagonists were N-terminal truncated fragments of the CGRP peptide [52]. $CGRP_{8–37}$, which includes all but the first seven amino acids of the normal peptide, functions as an antagonist of CGRP receptors by blocking binding of endogenous full-length CGRP. Although $CGRP_{8–37}$ has been demonstrated to inhibit vasodilation and neurogenic inflammation in animal models, its clinical effectiveness is severely limited due to its short half-life [53] that contributes to its lack of potency *in vivo*. While other truncated CGRP analogs with higher affinities for CGRP receptors have been developed, they have also not proven useful in clinical studies because of similar limitations [54]. Although these results clearly demonstrated that truncated forms of CGRP might not be clinically useful, information gained from these studies provided convincing evidence to support the development of non-peptide molecules to inhibit CGRP receptor function for the treatment of migraine.

CGRP receptors are expressed by multiple different cell types within the nervous, cardiovascular, and immune systems that are thought to play important roles in migraine pathology. For example, CGRP receptors have been reported on neurons and glia in the peripheral and central nervous systems, including second order neurons and astrocytes [55, 56] as well as trigeminal ganglion neurons [35, 57] and satellite glial cells [34]. In addition, CGRP receptors are present on meningeal smooth muscle cells [58, 59] and the larger cerebral blood vessels [60, 61]. Another site of CGRP receptors is mast cells found within the dura mater [31, 62].

3. CGRP Receptor Antagonists

3.1 Olcegepant (BIBN4096BS)

The first potent and selective non-peptide antagonist of the human CGRP receptor was originally referred to as BIBN4096BS, but has been renamed olcegepant [63, 64]. The particular affinity of olcegepant for the CGRP receptor has been shown to dependent on residues within the extracellular region of RAMP1 rather than the CLR or RCP subunits [48].

Since this site is required for selective binding of CGRP, olcegepant functions as a CGRP receptor antagonist by directly competing for the binding site of the endogenous ligand CGRP and therefore, inhibits the physiological and cellular effects of CGRP. Information obtained from *in vitro* and animal studies, which have recently been summarized in several comprehensive review articles [65, 66], demonstrated that olcegepant could repress the stimulatory effects of CGRP on isolated and intact blood vessels [67–69]. However, olcegepant was shown to lack vasoconstrictive effects based on a study in which infusion of olcegepant to healthy volunteers caused no significant systemic or cerebral blood flow changes [70]. More recently, olcegepant was shown to suppress the stimulatory effect of CGRP on its own synthesis in trigeminal ganglion neurons, an event thought to function in an autocrine manner such that CGRP release from neuronal cell bodies stimulates its own further synthesis [71].

Importantly, results from a phase IIa clinical trial on olcegepant provided the first direct evidence to support the use of a non-peptide CGRP receptor antagonist as an abortive therapy of migraine [30]. Findings from that clinical proof-of-concept study not only demonstrated that olcegepant was as effective as oral triptans, which are regarded as the most effective class of abortive anti-migraine drugs, but also demonstrated its safety and minimal adverse event profile [72]. In particular, the finding that olcegepant appeared to lack cardiovascular side effects such as changes in basal blood pressure or heart rate [30, 67] may prove to be advantageous for this new class of compounds. While results from clinical studies demonstrated that olcegepant was effective in treating spontaneous migraine attacks [30] and CGRP-induced headache [73], a major limitation for the usefulness of this hydrophilic compound was that fact that it had to be administered by intravenous injection.

4.2 Telcegepant (MK-0974)

To facilitate a more useful delivery method, Merck Research Laboratories undertook a research program to discover compounds that were potent oral CGRP receptor antagonists [74]. One compound that was identified using this approach was the selective CGRP receptor antagonist, MK-0974, which has now been renamed telcagepant [75]. Findings from pharmacological studies have shown that telcagepant is a highly selective, potent oral antagonist of the human CGRP receptor [76, 77]. Telcagepant, at nM concentrations, has been reported to repress CGRP stimulated cAMP responses in HEK293 cells that express the human CGRP receptor [78]. The efficacy and safety profile of telcagepant in the acute treatment of migraine was initially demonstrated in a phase II clinical [79]. In that study, telcagepant (MK-0974) was shown to be effective and generally well-tolerated for treating moderate to severe migraine attacks with a primary endpoint of pain relief at 2 hours [79, 80]. The reported outcomes for telcagepant were comparable to those of rizatriptan and were significantly superior to placebo. Telcagepant also displayed superior efficacy vs. placebo for secondary endpoints such as sustained pain relief at 24 hours and sustained pain freedom at 24 hours as well as providing relief of migraine-associated symptoms such as photophobia, phonophobia and nausea. Furthermore, the incidence of the most often reported adverse events for telcagepant, which included nausea, dizziness, and somnolence, were similar to the placebo group. Similar results, such as efficacy similar to triptans and few associated adverse events, were obtained from a larger randomized, parallel-treatment, placebo-controlled, double-blind, trial conducted at sites in both Europe and the United States of America [79]. More definitive proof for the efficacy of telcagepant was recently provided by data from a large phase III clinical trial [81]. Results from this study clearly demonstrate the effectiveness of telcagepant to relieve the pain and other migraine symptoms at 2 hours as well as providing sustained pain relief for up to 24 hours. In addition, telcagepant was found to be generally well tolerated.

Despite the positive clinical data supporting the use of telcagepant in the acute treatment of migraine, Merck Research Laboratories recently issued a press release stating that the company will not file an application to the FDA for telcagepant in 2009. The decision to suspend further development and testing of this compound was based on findings from a phase IIA exploratory study in which a small number of patients taking telcagepant twice daily for three months for the prevention of migraine had marked elevations in liver transaminases [82]. Thus, it will be important to determine whether the liver toxicity is related to the particular compound, which is a member of the azepanone-based family of CGRP receptor antagonists, or whether it is a class effect. Encouragingly, other members of this family have recently been modified to retain the potency of telcagepant and yet minimize the susceptibility to oxidative metabolism believed to be involved in hepatic toxicity [83].

4. CGRP receptor antagonists: numerous cellular targets for migraine therapy

Given the localization of functional CGRP receptors on multiple diverse cell types implicated in the underlying pathology of migraine, the beneficial effects of CGRP receptor antagonists in the acute treatment of migraine likely involves repressing the function of cells located in peripheral tissues as well as in the CNS (Table 1). Based on preclinical data, blocking CGRP receptor activation would be expected to affect the function of vascular smooth muscle cells, mast cells, trigeminal ganglion neurons, glial cells, and second-order neurons within the CNS. If the headache phase of migraine is dependent on nociceptive input from perivascular sensory nerve fibers as recently proposed [84], then inhibiting dilation of human cerebral and meningeal vessels, which express functional CLR and RAMP1 proteins [58, 59], by blocking CGRP receptor function would be beneficial. Similarly, inhibiting activity of CGRP receptors that are expressed by dural mast cells [31] would prevent mast cell degranulation and the subsequent release of histamine and other pro-inflammatory agents known to cause peripheral sensitization of trigeminal nociceptors [85]. Other likely peripheral targets of CGRP antagonists would be the neuronal cell body and associated satellite glial cells located within the trigeminal ganglion since both of these cells express functional CGRP receptors [71, 86, 87]. While blocking the CGRP receptors on trigeminal neuron cell bodies would prevent further synthesis of CGRP, inhibition of CGRP receptors on satellite glial cells would repress the stimulated release of cytokines as well as nitric oxide [34, 86, 87], which can cause sensitization and activation of trigeminal neurons [58, 59, 88, 89]. Thus, CGRP antagonists would function to block further production and release of CGRP from trigeminal neurons by both direct as well as well indirect mechanisms. Inhibition of CGRP receptors on second order sensory neurons within trigeminal nuclei in the caudal brain stem and upper cervical spinal cord [56] would directly block further nociceptive signaling in the CNS and, thus, prevent the development of central sensitization and hyperalgesia. Furthermore, CGRP antagonists might also function to directly inhibit NMDA-evoked membrane currents and even reverse sensitization of nociceptive neurons located in the laterocapsular part of the central nucleus (CeLC) [90, 91], which is the target of the spino-parabrachio-amygdaloid pain pathway [92]. In addition, CGRP antagonists would be expected to block stimulation of astrocytes and microglia, which play prominent roles in central sensitization and persistent pain at the level of the TNC [93–98]. Taken together, CGRP receptor antagonists would be predicted to inhibit cellular events that lead to peripheral sensitization and activation of trigeminal ganglion neurons as well as central sensitization of nociceptive neurons in the TNC and amygdala. Thus, blockage of CGRP receptors would be expected to inhibit the inflammatory and nociceptive effects of CGRP at multiple sites within the peripheral and central nervous systems that are implicated in the underlying pathology of migraine.

Based on the localization of CGRP receptors in different regions of the brain thought to inhibit nociception, not all the actions of a CGRP receptor antagonist would be expected to exert an anti-inflammatory or anti-nociceptive effect (Table 1). This might be especially true for antagonists that can readily cross the blood brain barrier and thus, directly affect neurons in regions within the brain. Interestingly, CGRP receptors are present on neurons located in the nucleus raphe magnus, periaqueductual grey, nucleus accumbens, and central nucleus of amygadala, which are all thought to inhibit nociception in response to noxious stimuli [99]. Thus, it might be proposed that CGRP receptor antagonist might actually worsen a migraine attack by blocking the anti-nociceptive actions of these neurons. However, data from clinical studies on olcegepant and telcagepant do not support such a direct role. Indeed, additional studies are required to more clearly delineate the physiological effects of blocking CGRP receptors within the brain.

5. Conclusions

Based on experimental and clinical studies, CGRP is believed to play an important role in the generation of pain during migraine attacks by facilitating cellular events that contribute to sensitization of peripheral and central neurons involved in nociceptive transmission. In support of a central role of CGRP and activation of its receptor in migraine pathology, the non-peptide CGRP receptor antagonists olcegepant and telcagepant have been shown to be effective in the acute treatment of migraine. Unfortunately, both compounds are no longer being pursued as frontline abortive migraine drugs. However, data from the clinical studies on these compounds has clearly demonstrated the potential therapeutic benefit of this class of drugs and supports the future development of CGRP antagonists to treat migraine and possibly other types of chronic pain.

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Table 1

Proposed function of CGRP antagonists based on localization of RAMP1 location and/or functional CGRP receptors.

Location	Cell Type	Proposed Function of CGRP Antagonist Binding
Dura	Smooth muscle cells	Block vasodilation of meningeal vessels, decrease inflammatory response
Dura	Mast cells	Prevent mast cell activation and secretion of vasoactive, inflammatory, and sensitizing molecules (Lennerz et al., 2008)
Trigeminal ganglion (TG)	Neurons	Suppress sensitization of primary afferents
TG	Satellite glia	Repress sensitization and activation of primary nociceptive neurons
Trigeminal nucleus caudalis(TNC)	Neurons	Inhibit sensitization of second order neurons (Williamson et al., 2001)
TNC	Astrocytes	Repress astrocyte activation and stimulation of c-fos and cAMP (Reddington et al., 1995)
TNC	Microglia	Suppress microglial activation and stimulation of c-fos and cAMP (Reddington et al., 1995)
Laterocapsular part of central nucleus (CeLC)	Neurons	Inhibit NMDA-evoked membrane currents, reverse sensitization of nociceptive CeCL neurons (Han et al., 2005)
Nucleus raphe magnus(NRM)	Neurons	Post-synaptic inhibition of nociception in the dorsal longitudinal tract (Yu et al., 2009)
Periaqueductal grey (PAG)	Neurons	Block descending analgesic pathway to the dorsal horn of the spinal cord (Yu et al., 2009)
Nucleus accumbens (NaC)	Neurons	Binds endogenous CGRP to induce antinociception during noxious stimulation (Yu et al., 2009)
Central nucleus of amygdala (CeA)	Neurons	CGRP innervation of met-enkephalin-ergic neurons projecting from CeA to PAG (Yu et al., 2009)