

## THE PHARMA INNOVATION - JOURNAL

# Role of Calcitonin Gene-Related Peptide (CGRP) in Migraine: A Review

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The neuropeptide calcitonin gene-related peptide (CGRP) has long been postulated to play an integral role in the pathophysiology of migraine. While clinical findings are consistent with such a role, the specific pathogenic mechanisms of CGRP in migraine have remained speculative until recently. Through advances in molecular neuroscience, the pathogenic mechanisms of CGRP in migraine have begun to be elucidated. This paper discusses the hypothesized role of CGRP in migraine and reviews recent findings on the molecular mechanisms of this neuropeptide in migraine pathophysiology.

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*Keyword:* CGRP, Migraine, Neuropeptide, RAMP Proteins, Neurovascular Disorder.

### 1. Introduction

Migraine is defined as a neurovascular disorder affecting more than 10% of the global population with a prevalence of 15-18% in females and 6-9% in males. The disorder associated with dysfunction of the cerebral nerves and blood vessels<sup>[2,3]</sup>. Although early theories posited the cerebral blood vessels as the site of origination of migraine attacks, current hypotheses place the primary dysfunction in the brain-probably in brainstem centers important in regulating vascular tone and pain sensation. Neurological symptoms including photophobia, phonophobia, scintillations, numbness and weakness are common.

Episodic migraine attacks, although at times disabling<sup>[4]</sup>, may be well controlled with acute anti-migraine medications, but between 2.5 and 14% of patients with episodic migraine develop chronic migraine over the course of one year<sup>[5,6]</sup>. Chronic migraine is defined as fifteen or more days with headache per month for more than

three months with particular features, such as nausea, photophobia and phonophobia, or triptan/ergotamine treatment, on a proportion of those days<sup>[7]</sup>. The progression from episodic to chronic migraine is sometimes referred to as migraine transformation<sup>[8]</sup> or “chronification”. Chronic migraine is frequently regarded as refractory to medical management by headache experts, and has a significant impact on the patient’s life and society. Migraine can be triggered by both internal and external triggers. In early studies migraine was first seen as a vascular disorder<sup>[9]</sup> and then as a neurogenic disorder<sup>[10,11]</sup>. In current hypotheses, migraine-specific triggers cause primary brain dysfunction, which causes dilation of cranial blood vessels that are innervated by sensory fibers of the trigeminal nerve to dilate<sup>[2,3]</sup>. The dilated blood vessels mechanically activate perivascular trigeminal sensory nerve fibers.

Activation of trigeminal sensory nerve fibers causes a pain response to be conveyed to the

brainstem (and from there to higher brain centers) and evokes release of vasoactive peptides such as substance P and CGRP from trigeminal fibers. These peptides exacerbate vasodilation and cause neurogenic inflammation characterized by vasodilation, leakage of blood vessels, and degranulation of mast cells<sup>[12]</sup>.

The vasodilation and neurogenic inflammation further increase activation of the sensory trigeminal fibers, perpetuate the release of vasoactive peptides including CGRP, and modulate transmission of pain impulses to the brain. As migraine progresses, the brainstem and spinal cord centers that are the first to receive the pain impulses from the trigeminal nerve are hypothesized to become sensitized with a resultant worsening of headache pain and increased sensitivity to environmental and other stimuli<sup>[3]</sup>.

### 1.1 CGRP in Migraine

The complexity and heterogeneity of migraine, a neurovascular disorder, has hindered a systematic study of the underlying mechanisms. Despite these hurdles, major advances have taken place in the past decade leading to a better understanding and treatment of migraine<sup>[13]</sup>. Multiple studies have progressively directed attention at the neuropeptide calcitonin gene-related peptide (CGRP)<sup>[14,15,16]</sup>.

CGRP is a 37 amino acid neuropeptide and a potent vasodilator neuropeptide, which also has a role in the transmission of nociceptive information<sup>[17, 18, 19, 20]</sup>.

CGRP is a multifunctional peptide, a major modulator of the cardiovascular system<sup>[21,22]</sup> and a key promoter of neurogenic inflammatory pain<sup>[14]</sup>, as well as modulating nociceptive input via central pathways<sup>[23]</sup>. There are two forms of this peptide, aCGRP, which is predominantly expressed in the nervous system and bCGRP, which is primarily expressed in the enteric sensory system.

In the central nervous system (CNS), CGRP is expressed in several regions such as the striatum,

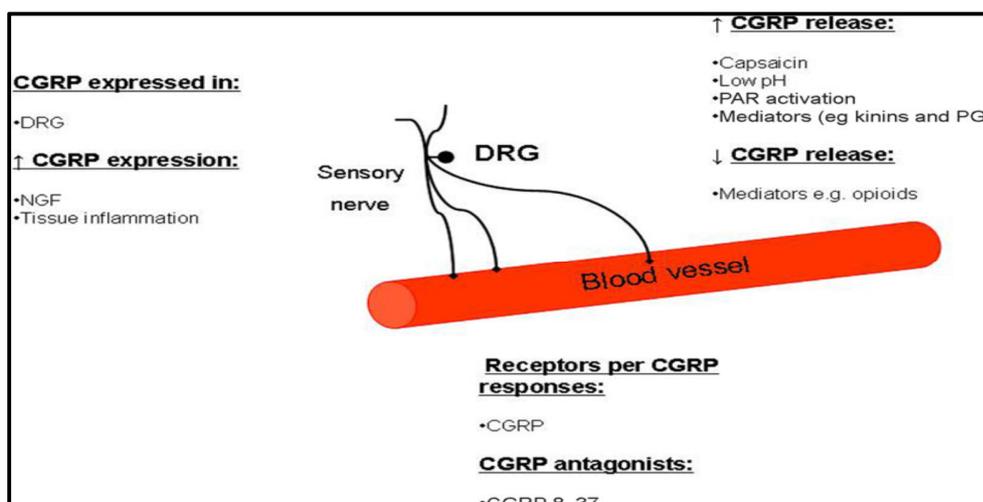
amygdale, hypothalamus, colliculi, brainstem, cerebellum and the trigeminal complex<sup>[24, 25]</sup>.

Moreover, CGRP is found in primary spinal afferent C and Ad fibres, which project to the brainstem. CGRP acts at second-order neurons in the trigeminal nucleus caudalis (TNC) and at C1-2 levels, to transmit pain signals to the thalamus and higher cortical pain regions<sup>[26]</sup>. Early autoradiographic studies have shown CGRP-binding sites in the rat cerebellum, hippocampus, amygdala, cortex, brainstem and spinal cord<sup>[27,28]</sup>. CGRP was identified in 1982 when Rosenfeld *et al* (1983)<sup>[29]</sup> showed that alternative RNA processing of the calcitonin gene generated mRNAs encoding a peptide they named CGRP. It is highly expressed in certain nerves and is now known to belong to a family that includes the more recently discovered peptides adrenomedullin and amylin. This group belongs to a larger family of peptides that includes calcitonin.

Calcitonin is a potent inhibitor of bone resorption, acting via receptor-mediated inhibition of osteoclast function<sup>[30]</sup>. The overall effect of CGRP on bone resorption is unclear, although it can inhibit osteoclast activity,<sup>[31]</sup> but it is best known for its potent cardiovascular effects<sup>[32]</sup>.

CGRP is distributed throughout the central and peripheral nervous systems and exhibits a range of biological effects on tissues including those associated with gastrointestinal, respiratory, endocrine, and central nervous systems (Fig1)<sup>[33,40]</sup>.

In fig. 1 The CGRP gene is expressed in the dorsal root ganglion (DRG) and is upregulated by factors that include nerve growth factor (NGF) and tissue inflammation. CGRP is released from nerves in response to several stimuli, such as capsaicin and low pH, proteinase-activated receptor (PAR activation), and mediators (eg, kinins and prostaglandins [PG]). Opioids can inhibit the release of CGRP. The response to CGRP is inhibited by CGRP receptor antagonists. Several seminal studies support the pivotal role of CGRP in migraine:



1. Initially, CGRP levels were found to be elevated during spontaneous and nitroglycerin-induced migraine [41, 42] and reduced by sumatriptan, coincident with pain relief [12]. However, a recent well controlled study has questioned whether CGRP levels are increased during migraine attacks [43]. This unresolved question may be explained by the reports of higher plasma CGRP levels outside of a migraine attack in migraineurs when compared with nonheadache control individuals [44, 45].
2. Subsequently, intravenous administration of CGRP was found to induce a delayed migraine-like headache in migraineurs [46] but not in control individuals [47]. On the contrary, a recent study evaluating the effect of CGRP as a migraine trigger in patients with familial hemiplegic migraine (FHM) found that a small group of genetically well-defined patients were not hypersensitive to CGRP [48]. An important consideration is that FMH patients also failed to demonstrate the hypersensitivity to glyceryl trinitrate (GTN), a known migraine trigger [49, 50]. In a thorough review of the role of nitric oxide in primary headaches, Olesen has discussed the potential connection between the nitric oxide and CGRP pathways, which remains controversial [51]. In addition to these studies, Edvinsson & Edvinsson did not find differences in peripheral microvascular

sensitivity to CGRP and nitric oxide in migraineurs and healthy controls [52]. One possible explanation for the hypersensitivity observed in patients with common forms of migraine is that central actions of CGRP and nitric oxide may be more relevant in migraine than their peripheral actions.

3. Finally, a proof of concept study demonstrated that CGRP receptor antagonists are effective in the treatment of the headache and associated symptoms of a migraine attack [53]. This finding has now been extended with a second antagonist in clinical trials described over the past year [54, 55].

The potential role of CGRP in migraine pathophysiology was suggested 20 years ago [56, 57], and several studies have since then revealed the correlation between migraine and cranial release of CGRP. Experimental and clinical studies have shown that there is an increased level of trigeminal system-released CGRP during migraine attacks [58, 12, 41]. The most important evidence for the role of CGRP in migraine pain came recently from the development of CGRP-receptor antagonists [54, 55, 53].

### 1.2 CGRP- Receptor:

The CGRP receptor is a relatively unique G protein coupled receptor that is a multimer of the CLR, RAMP1 and receptor component

protein<sup>[59]</sup>. RAMP1 is a small single-transmembrane protein that is required for CGRP binding by CLR [52–54]. In addition to ligand specificity, RAMP1 also influences CLR glycosylation and cell surface trafficking. RAMP1 by itself may represent an attractive drug target in the near future<sup>[60]</sup>. The crystal structure of the human RAMP1 extracellular domain has just recently been described by<sup>[61]</sup>, which should facilitate future RAMP1 drug designs. Interaction of CLR with two other RAMP proteins, RAMP2 or RAMP3, yields adrenomedullin receptors. The CGRP receptor can activate multiple signal transduction pathways, although it is most commonly coupled to G $\alpha$  to increase cAMP levels<sup>[59,60]</sup>. In vascular smooth muscle, these paths lead to activation of potassium channels and relaxation. The relevant downstream targets in migraine are not known, but will likely be an area of increasing interest.

In the past year, Hay's group performed a reciprocal mutation analysis of the three RAMP proteins that built on previous mutation and chimeric studies<sup>[63]</sup>. The findings extended our appreciation for the importance of residue 74 in RAMP1 and its corresponding residues in RAMP2 and RAMP3 for ligand specificity and binding of the antagonist BIBN-4096BS. However, more importantly the lack of clear roles for other residues that differ between the RAMPs hint at the complexity of interactions between CLR and RAMP1 to generate the CGRP receptor. A potentially relevant development in the migraine field is a new mouse model with overexpression of human RAMP1 in the nervous system. These mice are sensitized to CGRP induced plasma extravasation, a measure of neurogenic inflammation, and may represent a valuable model for the study of migraine pathophysiology and a tool for future drug development<sup>[64,65]</sup>.

### 1.3 CGRP- Receptor Antagonists

The CGRP-receptor antagonists are a new class of antimigraine drug, which act by blocking the action of CGRP on the CGRP-receptor complex (Figure 1). The receptor for CGRP has been identified as a G-protein-coupled receptor of the

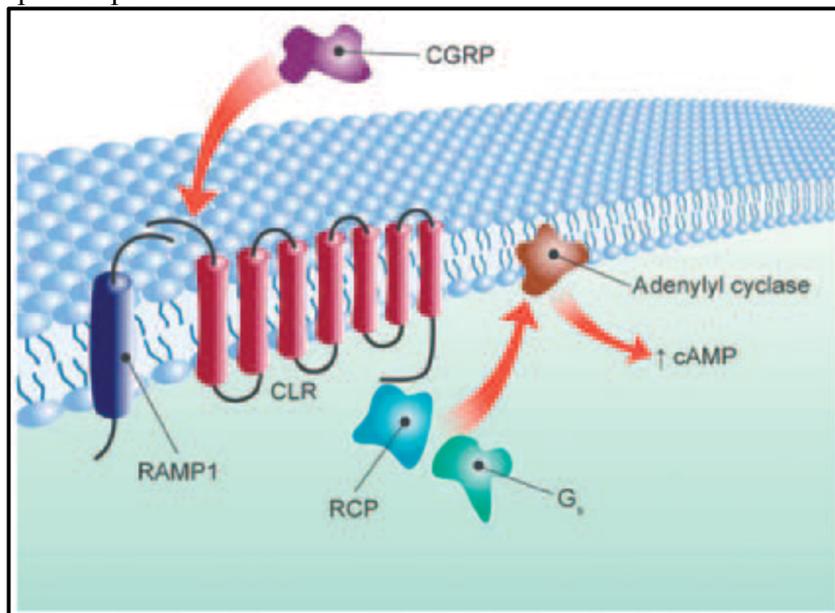
B-subtype<sup>[66]</sup>. The functional receptor consists of a complex of a seven transmembrane spanning protein, calcitonin receptor-like receptor (CLR), a single transmembrane- spanning protein designated receptor activity modifying protein (RAMP)1<sup>[67]</sup>, and an intracellular protein, receptor component protein (RCP)<sup>[68]</sup>.

RAMP1 is involved in receptor trafficking and is required for CGRP binding to CLR, whereas the interaction of CLR with other RAMP proteins, RAMP2 or RAMP3, forms adrenomedullin receptors<sup>[64,67,69]</sup>. Olcegepant (BIBN4096BS) was the first developed CGRP-receptor antagonist that showed clinical efficacy in intravenously administered treatment of acute migraine<sup>[70]</sup>. However, due to its low oral bioavailability, the development of this compound was terminated. Recently, telcagepant (MK-0974) was developed and is the first orally active CGRP-receptor antagonist that is effective in the acute treatment of migraine (Edvinsson and Linde, 2010b)<sup>[71]</sup>. In phase III trials, acute use of telcagepant was shown to have fewer side-effects than the currently used antimigraine drugs, 5-hydroxytryptamine (HT) 1B/1D agonists (triptans)<sup>[55,55]</sup>. The most important difference from the triptans is that telcagepant does not appear to constrict intracranial<sup>[72]</sup> or coronary blood vessels<sup>[73,74]</sup>. The CGRP-receptor antagonists have opened a possible new option in migraine treatment<sup>[75]</sup>.

Consequently, many scientific questions have arisen, which need to be addressed. It is of great importance to clarify where the CGRP receptor is expressed and on which possible sites telcagepant has its therapeutic effect. The trigemino-vascular system is without doubt an interesting area for this because of its important role in migraine pathology<sup>[76]</sup>. Recent data demonstrate that there are several regions in the CNS that could play a role in nociception and in migraine pathology.

The fig. 2 shows the schematic view of the CGRP receptor with its components. The receptor for CGRP is a G-protein-coupled receptor of the B-subtype. The functional receptor consists of CLR, RAMP1 and RCP. CGRP: calcitonin gene-related peptide; CLR: calcitonin receptor-like receptor;

RAMP1: receptor activity modifying protein 1;  
RCP: receptor component protein.



### 1.4 Other Important Biological Functions of Calcitonin Gene-Related Peptide

CGRP has other important functions beyond the nervous system.

Using CGRP-knockout mice,<sup>[77]</sup> have found a role of endogenous CGRP promoting tumor-associated angiogenesis and tumor growth. Another recent study supports the cardioprotective role of CGRP against ischemia/reperfusion injury <sup>[78]</sup>. These and other functions are important considerations when developing therapeutic strategies targeting CGRP or its receptor. Drug-induced upregulation or downregulation of the receptors leading to changes in their response to endogenous CGRP may have deleterious effects in other organs or systems.

### 2. Conclusion

Recent clinical and basic research advances have helped clarify the role of CGRP in migraine, although there are still many unanswered questions in the field. CGRP receptor antagonists are emerging as the new generation of migraine drugs. With increased availability of genetic diagnostic tools, it is foreseeable that future research will attempt to examine genetic susceptibility to migraine by studying the CGRP

and CGRP receptor genes. From the therapeutic perspective, a novel approach to repress CGRP expression may be through posttranscriptional gene silencing. The therapeutic use of RNAi in neurological diseases is currently being explored and may not be far from the bedside <sup>[79]</sup>.

### 3. Research in Progress

Basic and clinical researchers continue to offer complementary approaches that are improving our understanding of the role of CGRP in the complex pathogenesis of migraine. Even though the story is far from complete, we propose that activation of a peripheral inflammatory response by CGRP acting in concert with central modulation by CGRP contributes to migraine pain. Several new CGRP-based therapies are currently under development for the treatment of migraine. New small-molecule CGRP receptor antagonists have completed Phase II clinical trials, both with positive results <sup>[80, 81]</sup>. Monoclonal antibodies intended to prevent CGRP from engaging its receptor are being pursued as a path towards long-term prophylactic therapy <sup>[82, 83]</sup>. In preclinical studies, these antibodies were able to inhibit neurogenic inflammation without affecting cardiovascular parameters <sup>[83]</sup>. If effective in migraine therapy, systemic delivery

of antibodies will highlight the importance of peripheral CGRP actions. Additional antimigraine therapies are also being developed targeting glutamate receptors, which as mentioned above could potentially be modulated by CGRP [84, 85].

Future research will probably explore other molecules that might contribute to the pathogenesis of migraine, such as histamine and proCT. It seems likely that experiments will continue to examine the relationship between the nervous and immune systems, especially the interplay of CGRP with the immune system. The identification of sites of CGRP action in the CNS should lead to more insights and improved therapeutics for migraine. In this way, increased understanding of the impact of CGRP on the trigeminovascular system will continue to propel us closer to successful therapeutics for migraine.

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