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Calcitonin gene-related peptide (CGRP): Role in migraine pathophysiology and therapeutic targeting

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Abstract

Introduction: The neuropeptide calcitonin gene-related peptide (CGRP) is recognized as a critical player in migraine pathophysiology. Excitement has grown regarding CGRP because of the development and clinical testing of drugs targeting CGRP or its receptor. While these drugs alleviate migraine symptoms in half of patients, the remaining unresponsive half of this population creates an impetus to address unanswered questions that exist in this field.

Areas covered: We describe the role of CGRP in migraine pathophysiology and CGRP-targeted therapeutics currently under development and in use. We also discuss how a second CGRP receptor may provide a new therapeutic target.

Expert opinion: CGRP targeting drugs have shown a remarkable safety profile. We speculate that this may reflect the redundancy of peptides within the CGRP family and a second CGRP receptor that may compensate for reduced CGRP activity. Furthermore, we propose that an inherent safety feature of peptide-blocking antibodies is attributed to the fundamental nature of peptide release, which occurs as a large bolus in short bursts of volume transmission. These facts support the development of more refined CGRP therapeutic drugs, as well as drugs that target other neuropeptides. We believe that the future of migraine research is bright with exciting advances on the horizon.

Keywords

migraine; CGRP; gepants; monoclonal antibodies; trigeminovascular system

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Declaration of interest

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1. Introduction

Migraine is a complex neurovascular disorder. The International Headache Society defines migraine as a headache lasting 4–72 hours that presents with multiple sensory abnormalities such as pain and photophobia (Table 1) [1–4]. Affecting 15% of all people, migraine is more common in women relative to men and is the second most disabling disease in the world according to the World Health Organization [5]. Globally, over 1 billion people are thought to suffer from migraine [5, 6]. As a result, headache is one of the top 5 reasons people visit the emergency room [6].

Over the past 30 years, both clinical and preclinical studies have documented the role of the neuropeptide calcitonin gene-related peptide (CGRP), the most potent vasodilatory peptide known, in migraine pathophysiology [7]. While there are two forms of CGRP, αCGRP and βCGRP, they have similar activity, so we will simply use the term CGRP [7]. CGRP is widely expressed through both the peripheral and central nervous system (CNS) [8]. In the trigeminovascular system, CGRP is released from nerve fibers running along meningeal and cerebral arteries [9] and blood vessels [10]. CGRP can also be released in the trigeminal ganglion where about half the neurons have CGRP immunoreactivity [11]. In the CNS, CGRP-containing neurons can be found in the superficial layers of the spinal trigeminal nucleus, the locus coeruleus, the raphe nuclei, some nuclei of the thalamus and the cerebellum, to name a few [11–14]. It is important to note that CGRP does not apparently cross the blood brain barrier (BBB) [8].

Clinical studies provided evidence that, at least in some patients, CGRP was both necessary and sufficient to induce migraine. CGRP levels are elevated in the plasma [15, 16], saliva [17] and tear fluid [18] of patients during spontaneous migraine attacks and in the plasma during nitroglycerin-evoked migraine attacks [19]. However, not all studies demonstrated elevated plasma levels during attacks [20]. Interictal elevation of CGRP has also been reported in the tears of episodic and chronic migraine patients [18], and in the plasma [21] and cerebrospinal fluid [22] of chronic migraine patients. Not only are CGRP levels elevated during and between migraine but, when CGRP was infused into migraine patients, most developed a delayed migraine-like headache, whereas patients who do not get migraine only got a mild headache [23–26]. Sumatriptan can reverse some of these CGRP induced phenotypes. For example, elevated CGRP levels are normalized after sumatriptan administration in migraine patients [15], and following CGRP infusion, the resulting increased vasodilation and delayed headaches were treated with sumatriptan. This suggests that at least some of the anti-migraine effects of sumatriptan are through a CGRP-dependent pathway [27, 28]. Other agents can induce migraine-like headaches including pituitary adenylate cyclase-activating polypeptide (PACAP) [29] and nitric oxide donors such as nitroglycerin [19] or sodium nitroprusside [30]. Interestingly these substances all have strong vasodilatory effects. However, not all vasodilators can induce migraine headache. Specifically, vasoactive intestinal peptide (VIP) induces vasodilation but does not induce migraine, suggesting that the vasodilation induced by CGRP is by itself not solely responsible for migraine [31]. However, as discussed later, this could be due to the rapid break down of VIP relative to CGRP and PACAP [32].

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The need for this review is driven by the recent approvals of CGRP-targeted drugs that has occurred with relatively little understanding of how the drugs are working or why they have been safe so far. Thus, it is important to stay current in findings on how CGRP is involved in migraine pathophysiology and potential adverse effects of those drugs. In this review, we will briefly cover the current theories of where and how CGRP may be acting in migraine, discuss CGRP receptors, and update the growing list of current CGRP targeted therapeutics. We will finish with our opinion on why these CGRP antagonist drugs appear safe so far and where the field goes from here.

2. CGRP and migraine

2.1. Where is CGRP acting in migraine?

CGRP has been shown to act both in the peripheral and CNS in preclinical studies and both sites are likely important in migraine pathophysiology (Figure 1). In the periphery, CGRP targets mast cells, blood vessels, glial cells, trigeminal afferents in the meninges, and neural cell bodies and satellite glia in the trigeminal ganglia (for review see Messlinger and Russo 2018) [33]. In the meninges, CGRP likely contributes to neurogenic inflammation by triggering the release of neuron sensitizing agents from mast cells, which in turn leads to increased vasodilation in the dura [34]. The modulation of neural activity in the meninges could trigger a feedback loop that ultimately results in peripheral sensitization of nociceptors [33]. The efficacy of systemically administered CGRP targeting monoclonal antibodies strongly supports a peripheral role of CGRP in migraine since the antibodies have very poor BBB permeability [35]. Overall, peripheral sensitization is critical for CGRP's actions and likely sets the stage for CGRP actions in the CNS.

Within the CNS, CGRP and its receptor are present in multiple pathways believed to play a role in migraine pathophysiology [8]. The trigeminal ganglion (located outside of the BBB) projects to the trigeminal nucleus caudalis (TNC) where second order neurons carry the signals to the posterior thalamic area (PTA). We use PTA as a term to encompass all nuclei in the posterior thalamic area. The PTA appears to be a sensory integration center that is abnormal during migraine. Neurons in the thalamus receive input from the TNC and retinal ganglion cells [36], and several key studies have demonstrated in rodents the importance of the PTA in the development of photophobia and highlight the PTA as a possible center for the integration of light and pain [36–38]. CGRP likely contributes to this pathway as both CGRP and its receptors are present in discrete nuclei of the PTA. This is further supported by a study showing that injection of CGRP into the PTA facilitates neuronal firing [38]. Moreover, somatosensory and nociceptive stimuli from ascending pathways converge on the CGRP producing neurons of the subparafasicular and intralaminar nuclei [39]. In humans, the posterior thalamus is known to be activated during migraine attacks and has altered functional connectivity with multiple brain regions [40, 41]. Taken together, these data suggest that pre- and post-synaptic neuromodulatory actions of CGRP that have been reported in other neural circuits [42], could contribute to a state where the PTA is hypersensitive to sensory stimuli.

Pathways contributing to this sensory sensitization are likely to involve the "general alarm" system of the parabrachial nucleus (PBN) [43, 44]. The PBN is a relay station for pain and

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other sensory input as it travels to the forebrain [43]. The PBN receives direct projections from the trigeminal nucleus, leading to the affective component of pain [45]. CGRP is abundant in the PBN and the PBN projects to multiple brain areas that are thought to be involved in migraine pathophysiology [43]. It is possible that altered signaling in this pathway could underly some of the hypersensitivity experienced during migraine. Peripheral and central actions of CGRP probably work in concert to induce migraine, and the complex nature of the disorder makes it improbable that just one of CGRP's action is solely responsible for inducing migraine.

2.2. How are the migraine actions of CGRP assessed?

Most of the mechanistic evidence concerning the involvement of CGRP in migraine comes from preclinical studies. CGRP is one of the most well-defined migraine triggers and can induce multiple migraine-like symptoms in animals that mimic CGRP in infusion in humans, including pain-like symptoms. Mechanical hypersensitivity is a common symptom of migraine [46] and can be reproduced in rodents after CGRP administration [47]. Dural administration of CGRP in mice induced periorbital touch hypersensitivity [48]. Intrathecal injection of CGRP induced hyperalgesia in the hindpaw in response to pinch in rats [49] and increased mechanical allodynia in mice [50]. While evoked pain phenotypes are well described preclinically, for many years there was no assay to measure spontaneous pain in animals. In 2010 Mogil and colleagues demonstrated that some types of pain could be assessed through facial grimace without having to evoke a response [51]. We used that assay to demonstrate that peripheral CGRP injection in mice could produce spontaneous pain that could be partially blocked with sumatriptan, suggesting the pain was migraine-like [52]. The eye-opening action unit proved to carry most of the weight for the grimace assay, and we were able to use a continuous objective measurement of eye closure to measure CGRP-induced grimace [52]. With this set of experiments, we also demonstrated that CGRP induced pain was light independent, which suggests that pain and light-aversion (another CGRP induced phenotype) are independent of each other.

Photophobia is one of the diagnostic criteria of migraine (Table 1). Photophobia occurs when ordinarily non-painful light becomes uncomfortable or painful. Patients with migraine are bothered by even dim light and want to escape bright environments [53]. This idea of using increased light sensitivity has translated well into a mouse model. Light aversion can be induced by both central and peripheral CGRP injection in wild-type mice, and it can be treated by triptans suggesting that light-aversive behavior in mice is migraine-like. This behavior requires a bright light stimulus (~25,000 lux) in wild-type mice. In a CGRP-sensitized mouse model that overexpresses human RAMP1 (the rate limiting component of the CGRP receptor) in the nervous system, only a low light stimulus of 55 lux is needed to induce light aversion after central administration of CGRP [54]. However, peripheral administration of CGRP in those mice didn't induce any light aversion with dim light, suggesting that neural CGRP receptors are not the rate-limiting site of action outside the CNS. Of importance, this light aversion behavior is not due to anxiety as mice show no difference in a light independent anxiety test (open field assay) [54–57]. One interesting feature of the light aversion assay is that mice do not move as much when injected with CGRP, but this is only seen in the dark side of the box [54–57]. This suggests that the mice

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are not sedated or that their motor activity is not impaired, since they move just as much as vehicle-injected animals in the light. The desire to go into a dark area and rest is consistent with human behavior.

2.3. CGRP-based treatments

In the past years, different molecules have been developed to block CGRP signaling in order to treat migraine symptoms. The first molecules to show potential were the CGRP receptor antagonists called “gepants”. These molecules have a high affinity for the canonical CGRP receptor and prevent CGRP binding and signal transduction. Gepants do not cause direct vasoconstriction [58–61], which is an advantage compared to triptans since the migraine population is known to have an increased prevalence of cardiovascular diseases [62]. Multiple clinical trials showed that intravenous and oral gepants alleviated migraine symptoms acutely (Table 2). In contrast, the prophylactic efficacy of gepants are still debatable as some clinical trials had to be interrupted because of adverse effects, and others are still ongoing (for review see Negro and Martelletti, 2019 [63] and Table 2). The development of several gepants was stopped for different reasons: olcegepant has a low oral bioavailability and telcagepant and MK-3207 were discontinued because of liver toxicity after frequent use [63].

Despite those initial safety concerns, the efficacy of gepants led to further efforts to develop safe CGRP blocking molecules. Three gepants remain in clinical development: rimegepant, ubrogepant and atogepant. In phase 2b clinical trials, efficacy of rimegepant to treat acute migraine was assessed with different endpoints such as pain free, migraine free, photophobia and phonophobia free, and nausea remission [64]. Intermediate doses of rimegepant (75, 150 and 300 mg) were found to be significantly more efficient than placebo. In addition, rimegepant did not show any effect on liver function, suggesting that it is safer than previously terminated gepants. Intriguingly, a higher dose of rimegepant (600 mg) did not significantly differ from placebo [64], and authors hypothesized that it was due to inherent variability present in the patients randomized to this dose group. Following this study, three phase 3, double-blind, randomized, placebo-controlled studies (NCT03235479, NCT03237845, NCT03461757), and a safety study (NCT03266588) [65–67] were started, for which the results are still awaited. Similarly, ubrogepant demonstrated a positive dose-response outcome in the treatment of acute migraine in a phase 2b, double-blind, randomized, placebo-controlled study [68], with minimum adverse effects. However, results from this study are dampened by the high response rate of the placebo group, and the limited number of patients included. Two phase 3, double-blind, randomized, placebo-controlled studies (NCT02867709, NCT02828020) [69, 70] were completed in December 2017 and February 2018. Preliminary results confirm the findings of the phase 2b study. Atogepant has a different chemical structure than other gepants and is currently tested for migraine prophylaxis [71]. The very first results from a phase 2b/3 study (NCT02848326 [72]) show that adults treated with atogepant had greater reduction from baseline in monthly migraine days on average, compared with those treated with placebo [73]. No serious adverse events related to treatment occurred. As we are writing this review, the first gepant (ubrogepant) was approved for acute treatment of migraine with and without aura by the FDA.

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Monoclonal antibodies against CGRP (fremanezumab galcanezumab, eptinezumab) and against CGRP receptor (erenumab) are another class of molecules able to block CGRP signaling. Three of these antibodies (fremanezumab, galcanezumab, and erenumab) have recently been approved by the FDA for the prophylactic treatment of migraine and a decision on a fourth (eptinezumab) is expected in 2020. About half of the patients receiving these antibodies experience a 50% reduction in migraine days (Table 2) [74–78]. Interestingly there has been no difference in efficacy between the antibodies, whether they sequester CGRP or bind to the receptor. Moreover, the antibodies still show efficacy for over a month after administration and therefore can be used as prophylactic drugs administered monthly or even quarterly to patients, which presents an advantage compared to daily oral administration for the gepants.

It appears that the newly designed CGRP-blocking drugs are quite safe so far. These safety concerns are serious since the vasodilatory action of CGRP could be critical during certain pathological states like stroke [79, 80]. From the many clinical trials and being on the market for almost a year, it appears that CGRP and CGRP receptor antibodies are safe and well tolerated. What is not known are the long-term effects of CGRP blockade, although it is encouraging that Amgen/Novartis found their antibody to be safe so far at the three-plus year point from an ongoing five-year open label study [81]. In addition, a study with patients with angina found no detrimental effect of the antibody [82]. This study however presents several limitations such as (1) the inclusion of 78% of male subjects in a predominantly female disorder, (2) the inclusion of patients suffering from stable angina pectoris, when patients suffering from a microvascular disease would better represent the population at risk, and (3) assessing the effects of the drug at an early time-point at which it is unsure if the receptor antibody has had time to affix the receptor [79]. Cardiovascular concerns are paramount since migraine patients are known to be at a high risk of stroke and cardiovascular disease (for review see Sacco and Kurth, 2014 [62]). Could blockade of CGRP increase the severity of stroke? In one recent case report, one patient developed an ischemic event following treatment with a CGRP antagonist drug [83]. However, no conclusion should be made from a single patient report. Long term studies on cardiovascular health are warranted, beginning with animal studies investigating the role of CGRP blockade on ischemia.

2.4. CGRP receptors, signaling, and regulation

CGRP belongs to a family of structurally related peptides among which two other major members are amylin and adrenomedullin. Amylin and CGRP have a close molecular composition which explains their overlapping activity at different receptors [84]. Structure, activity and trafficking of those peptides at their receptors have been extensively reviewed by the Hay and Walker labs [84–87]. Briefly, all receptors for this family are composed of a G-protein coupled receptor (calcitonin receptor-like receptor (CLR) or calcitonin receptor (CTR)) associated to an accessory protein (receptor activity-modifying protein (RAMP) 1, 2, or 3). A recent finding is that CGRP can bind and activate both CLR/RAMP1 (canonical CGRP receptor) and CTR/RAMP1 (amylin receptor 1 (AMY_1)) equally. As a result of the late discovery of CGRP binding AMY_1, the majority of migraine research has focused on the canonical CGRP receptor. This problem was exacerbated by the lack of properly

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validated antibodies for the detection of the different components involved in these pathways. It is therefore a common assumption that CGRP-blocking drugs only block signaling through the canonical CGRP receptor. Even antagonists designed to selectively bind to CLR/RAMP1 are at best “relatively selective”, and this selectivity depends on which agonist is used, and some molecules have not yet been properly investigated [86].

The signaling of CGRP receptors at the plasma membrane generally involves cAMP pathways, but MAP kinase and calcium pathways can also be recruited [88]. However, signaling does not end at the cell surface. The complex CLR/RAMP1-CGRP is internalized into endosomes in response to CGRP binding [89, 90]. A recent study demonstrated that the CGRP receptor can signal from endosomes and that blocking this signaling can have antinociceptive effects [91]. It is unknown whether this signaling is involved in migraine pathogenesis. While the complex CTR/RAMP1-CGRP is also internalized, this phenomenon does not always depend on activation by an agonist [92] and the possible endosomal signaling for this receptor has not yet been investigated.

2.5. Conclusion

Even after the approval of the first molecules targeting CGRP or its receptor, research is still ongoing to elucidate where and how CGRP is involved in migraine pathophysiology. Deepening our knowledge of CGRP signaling in both physiological and pathophysiological conditions is crucial to optimize current and future treatments for migraine.

3. Expert opinion

To date, the key findings in the field are that CGRP is necessary and sufficient to induce migraine in many patients and that drugs targeting CGRP or its receptor are effective in migraine treatment. In this section, we will speculate first on the safety issue of the monoclonal antibodies and then on where the field might now be headed.

How is it possible for a drug that blocks such a potent cardioprotective molecule to be safe? We think that the answer to this safety question is that there likely only a partial, not a full, blockade of CGRP function. The CGRP receptor antibody was designed to target the canonical CGRP receptor. However, as described above, CGRP can also bind a second receptor, AMY_1, with equal affinity and based on pharmacological studies the CGRP receptor antibody is predicted to only bind the canonical receptor and not AMY_1 [93]. Likewise, the most studied small molecule receptor antagonists, olcegepant and telcagepant, preferentially bind the canonical CGRP receptor over AMY_1 [94]. Thus, AMY_1 might provide a “safety valve” to maintain some CGRP activity, for example on the vasculature, even in the presence of the receptor antibody or antagonists. Moreover, if the CGRP receptor antibody had equal binding to the AMY_1 and CGRP receptors, there might be greater efficacy from targeting both receptors. However, the additional blockade of these receptors might also contribute to a decreased safety profile.

What about the apparently equally safe ligand antibodies? For the ligand antibodies, one reason may be due to the basic biology of peptide release and action by volume transmission [95]. When a neuron releases CGRP, it is released in a large bolus with an estimated 10,000

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peptides from a single dense core vesicle. With an estimated release of thousands of vesicles from a single neuron, there could be millions of peptides released in single burst. Hence, it seems likely that antibodies could blunt the spread or volume of CGRP from the release sites, but not completely block it.

For the receptor-targeted and ligand-targeted drugs, an additional safety valve could be redundancy within the CGRP family. Adrenomedullin also has vasodilatory activity [96]. Perhaps adrenomedullin, as well as other family members, including amylin, step up to help compensate for the reduced levels of CGRP signaling. Therefore, it is possible that the reassuring safety profile seen to date from CGRP receptor and ligand targeting drugs may be due to those drugs only partially blocking the actions of CGRP coupled with compensation from other CGRP family members.

There is plenty of need for additional migraine therapeutics since only about 50% of patients positively respond to CGRP blocking molecules [97], and on average, the patients who respond have only a two-fold reduction in headache days. Given that 57–77% of migraine patients get a migraine-like headache upon CGRP infusion [23–26, 98], it seems likely that there is still a large pool of patients who could benefit from improved CGRP therapeutics. Despite making great strides in our understanding of how CGRP contributes to migraine pathophysiology, we still do not fully understand where CGRP is being blocked to reduce migraine symptoms. The evidence to date is on the side of the peripheral action, since neither the small molecule antagonists or antibodies easily cross the blood brain barrier [76, 99–103]. In addition, some of the triptans (which can lower CGRP levels during a migraine episode) do not easily cross the BBB and the amount that does is not likely to be sufficient to induce a therapeutic effect [104, 105]. While there is a debate regarding a possible BBB break down during migraine attacks, recent evidence suggests this does not occur [104]. One interesting study done with a PET tracer (MK-4232, which is a validated ligand for the CGRP receptor) demonstrated that telcagepant could block less than 10% of the CNS receptor binding at therapeutic doses [106]. Besides the peripheral sites of action, is the small amount of drug penetrating the CNS enough to induce an effect? Some patients seem to respond to a single dose of antibody for a longer period than others. The possibility that those patients have a greater central penetration of the drug should be studied. If this was the case, then it would warrant the design and testing of molecules blocking CGRP signaling in the CNS. Admittedly, centrally-acting CGRP drugs might have greater side-effects, but they also might be more effective and may be helpful for other pain states involving central sensitization.

In addition to targeting central CGRP actions, a second and not mutually exclusive direction to take is to investigate the role of the AMY_1 receptor in migraine? It is possible that blocking AMY_1 may be more effective than blocking the canonical receptor for some patients. AMY_1 is expressed in the trigeminovascular system and CNS, but there is a dearth of knowledge surrounding its role in migraine pathophysiology. Likewise, if the AMY_1 receptor is involved in migraine, this raises the question whether the peptide amylin can also induce migraine symptoms similar to CGRP. Preclinical and clinical studies on a possible role of amylin are currently being pursued.

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In addition to CGRP, there is an abundance of other neuropeptides that could possibly play a similar role in migraine [107]. In particular, PACAP and its receptors represent promising targets as PACAP displays many of the same properties as CGRP. PACAP injection into humans can induce migraine-like headaches [108, 109]. PACAP antibodies are already in the pipeline and seem to have a promising future. However, the development of a PACAP receptor (PAC1) antibody was stopped because it was not efficacious for the treatment of migraine. While this is disappointing, it is possible that other receptors play a role in PACAP signaling. For instance, PACAP can bind and signal through the VIP/PACAP receptors. If PACAP signaling through those receptors contributes to migraine, it would suggest that the short acting nature of VIP is a likely explanation as to why VIP fails to induce migraine-like symptoms after infusion, and highlights the possibility that prolonged stimulation of receptors could contribute to migraine pathophysiology. Beyond PACAP, there are hundreds of neuropeptides that could act as neuromodulators [95]. Furthermore, pro-inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α have also been shown to be elevated in the serum of migraine patients [110, 111]. Delineating the role of these other peptides and pro-inflammatory cytokines and how their altered activities contribute to heightened sensory states will likely be a fruitful endeavor, undoubtingly leading to a more thorough understanding of migraine pathogenesis, and hopefully to new efficacious drugs.

In conclusion, the success of CGRP-targeting drugs as migraine therapeutics is an exciting story, especially for the patients. Yet, this represents not the end, but rather the beginning of the story. CGRP has set the precedent for looking deeper at how it acts and at other neuropeptides that help modulate bidirectional information flow between the senses of the body and the brain.

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Abbreviations

CGRP	calcitonin gene-related peptide
FDA	Food and Drug Administration
CNS	central nervous system
BBB	blood brain barrier
PACAP	pituitary adenylate cyclase-activating polypeptide
TNC	trigeminal nucleus caudalis
PTA	posterior thalamic area
PBN	parabrachial nucleus

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CLR	calcitonin receptor-like receptor
CTR	calcitonin receptor
AMY_1	amylin receptor 1
RAMP	receptor activity-modifying protein

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Article highlights

- Preclinical and clinical studies have shown that calcitonin gene-related peptide (CGRP) is a critical neuropeptide in migraine pathophysiology, but the mechanisms by which it is involved remain to be elucidated.
- Targeting CGRP or its receptor with antibodies or small molecules is very effective at alleviating migraine symptoms in about half of the patients.
- CGRP antagonizing drugs appear to be safe so far, however long-term open label studies are needed to confirm this safety profile.
- Better knowledge of the sites of CGRP action and signaling pathways is likely to lead to improved treatments for patients.
- A second CGRP receptor known as the amylin 1 receptor could be a novel target for migraine treatment.
- Targeting other neuropeptides, such as PACAP and amylin that have similar functions as CGRP, represents an additional avenue for alternative and/or complementary therapeutics.

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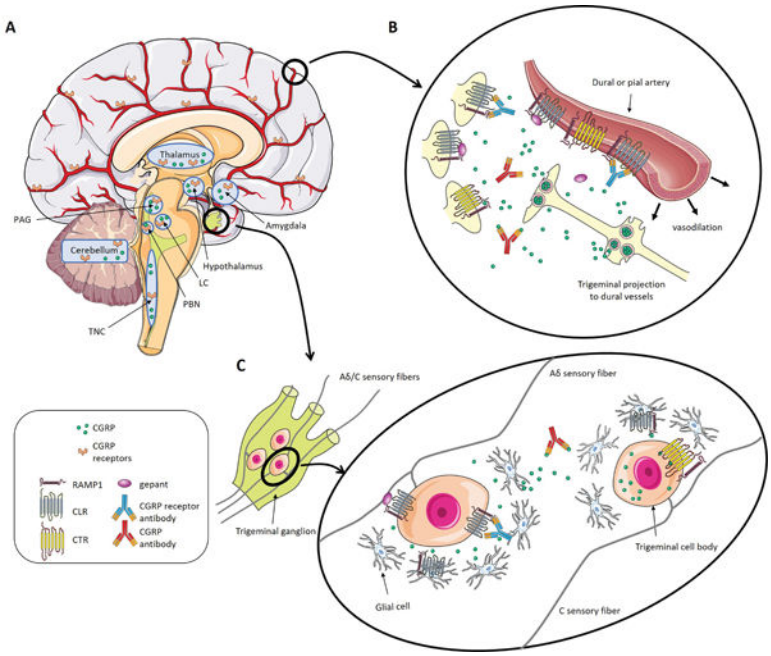

Figure 1.

CGRP and CGRP receptor distribution in the peripheral and central nervous systems. A) In the brain, CGRP and its receptors are present in the thalamus, the amygdala, periaqueductal grey, locus coeruleus, trigeminal nucleus caudalis, parabrachial nucleus, hypothalamus, and the cerebellum. The receptors can also be found at the meningeal vasculature. B) CGRP is released from trigeminal axons onto blood vessels in the meninges where it is involved in vasodilation and activation of trigeminal neurons. CGRP targeting drugs likely act at this site to treat migraine. C) CGRP is released in the trigeminal ganglion by small C fibers and binds to its receptors on other neurons (Aδ fibers) and glial cells triggering neurogenic inflammation. CGRP targeting drugs likely act at this site to treat migraine since the trigeminal ganglion is located outside of the BBB. While the AMY_1 receptor can also be found in the trigeminal ganglion, the CGRP receptor and the AMY_1 receptor do not seem to colocalize on the same neuron at this site [87]. CGRP and the CGRP receptor are rarely co-localized on the same neuron. At this point, it is still unknown if AMY_1 can be expressed on CGRP containing cells and our schematic representing both on the C fiber is still speculation. It is also unknown if the glial cells only express the CGRP receptor or also express AMY_1. The schematic art used in this figure were provided by Servier Medical art (http://servier.com/Powerpoint-image-bank).

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Table 1:

Diagnostic criteria for migraine from the International Classification of Headache Disorders, 3rd edition (beta version) [4].

A. At least 5 attacks fulfilling criteria B-D;
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated);
C. Headache has at least two of the following four characteristics:
a. unilateral location,
b. pulsating quality,
c. moderate or severe pain intensity,
d. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
a. Nausea and/or vomiting
b. Photophobia (light-induced discomfort) and phonophobia (sound-induced discomfort)

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Table 2:

CGRP targeting drugs: completed and ongoing trials.

Drug name, type of molecule	Indication (acute or prophylactic)	Development stage	References for clinical trials (type of migraine, number of treated subjects)
Olcegepant (BIBN 4096 BS), CGRP antagonist	Acute	Terminated for lack of oral availability	112 (episodic, 126 subjects)
Telcagepant (MK-0974), CGRP antagonist	Acute and prophylactic	Terminated for liver toxicity	113 (episodic, 1068 subjects) 114 (episodic, 1294 subjects) 115 (episodic, 683 subjects) 116 (episodic, 660 subjects) 117 (episodic, 1380 subjects) 118 (episodic perimenstrual, 3960 subjects) 119 (episodic, 330 subjects) 120 (episodic, 1677 subjects)
MK-3207, CGRP antagonist	Acute	Terminated for liver toxicity	121 (episodic, 547 subjects)
BI 44370 TA, CGRP antagonist	Acute	Terminated	122 (episodic, 341 subjects)
Rimegepant (BMS-927711), CGRP antagonist	Acute	Ongoing	64 (episodic, 799 subjects) 65 (episodic, not available at this time) 66 (episodic, not available at this time) 67 (episodic, 1375 subjects) 123 (episodic, 1186 subjects) 124 (episodic, not available at this time)
Ubrogepant (MK-1602), CGRP antagonist	Acute	FDA-approved	60 (healthy, 518 subjects) 68 (episodic, 640 subjects) 69 (episodic, 1672 subjects) 70 (episodic, 1254 subjects) 125 (episodic, 1672 subject) 126 (episodic, 1465 subjects)
Atogepant (AGN-241689), CGRP antagonist	Prophylactic	Ongoing	72 (episodic, 825 subjects) 127 (episodic, not available at this time) 128 (episodic, not available at this time) 129 (chronic, not available at this time) 130 (episodic, not available at this time)
Fremanezumab (TEV48125), CGRP monoclonal antibody	Prophylactic	FDA-approved	74 (high frequency episodic, 296 subjects) 131 (chronic, 264 subjects) 132 (healthy, 139 subjects) 133 (episodic and chronic, 133 subjects) 134 (healthy, 64 subjects) 135 (episodic, 874 subjects) 136 (high frequency episodic and chronic, 297 subjects) 137 (chronic, 1130 subjects)
Galcanezumab (LY2951742), CGRP monoclonal antibody	Prophylactic	FDA-approved	76 (episodic, 217 subjects) 138 (healthy, 63 subjects) 139 (episodic, 410 subjects) 140 (episodic, 915 subjects) 141 (episodic, 410 subjects) 142 (episodic, 862 subjects)
Eptinezumab (ALD403), CGRP monoclonal antibody	Prophylactic	Ongoing	75 (frequent episodic, 174 subjects) 143 (chronic, 588 subjects)
Erenumab (AMG 334), CGRP receptor monoclonal antibody	Prophylactic	FDA-approved	77 (episodic, 483 subjects) 144 (episodic, 383 subjects) 145 (chronic, 667 subjects) 146 (healthy and episodic, 108 subjects) 147 (episodic, 577 subjects) 148 (episodic, 965 subjects) 149 (chronic, 667 subjects)