Calcitonin gene-related peptide and migraine

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Purpose of review
Migraine is a common, complex disorder of the brain with significant morbidity. As the pathophysiology of the disorder has become better appreciated, the role of neuropeptides has been explored. Calcitonin gene-related peptide (CGRP) has emerged as a promising therapeutic target.

Recent findings
CGRP is widely distributed in the nervous system, particularly at anatomical areas thought to be involved with migraine, including the trigeminovascular nociceptive system. In studies, CGRP has been shown to be released during severe migraine attacks, and effective triptan treatment of an attack normalizes these levels. CGRP administration triggers migraine in patients and CGRP receptor antagonists can abort migraine. Moreover, recent data demonstrate that CGRP mechanism blockade either by small molecule receptor antagonists or by monoclonal antibodies can have a preventive effect in migraine.

Summary
This article highlights the evidence behind the role of CGRP in migraine and the state of CGRP-based mechanism treatment development. We present a summary of the evidence base behind CGRP in migraine pathophysiology and the novel CGRP mechanism drugs and their potential future contribution to migraine management in our clinical practice.

Keywords
calcitonin gene-related peptide, calcitonin gene-related peptide antagonists, gepants, migraine, monoclonal antibodies

INTRODUCTION
Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide which was discovered some 30 years ago [1]. It is derived from the gene encoding calcitonin and comprises two isoforms, alpha and beta CGRP [2]. CGRP is widely distributed in the nervous system, and particularly densely at anatomical sites known to be integral to the migraine process [3]. Within the central nervous system, these sites include the hypothalamus, cerebellum and brainstem [4]. Immunocytochemistry studies have shown that up to half of the trigeminal neurons produce CGRP within the trigeminal system, at various sites including the trigeminal ganglion, nerve endings and in higher order neurons and glia [5]. Centrally, CGRP is therefore involved in nociceptive transmission through second and third order neurons, and pain modulation in the brainstem, whereas peripherally it mediates vasodilatation through smooth muscle receptors [6].

Although animal studies have shown the role of several neuropeptides during trigeminovascular system activation, including substance P, vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide (PACAP) [7], only CGRP [8] and PACAP [9] seem to be released when durovascular structures are stimulated in the cat [8] and in humans. CGRP and PACAP, but not substance P, are elevated in the cranial circulation during acute migraine attacks [10]. These elevated levels normalize after effective triptan treatment of the migraine attack [11]. In chronic migraineurs, CGRP seems to be chronically elevated [12] and other human studies have shown that administering CGRP to a migraine sufferer triggers a migraine attack phenotypically similar to the patient’s spontaneous attack [13]. These studies over almost 30 years have confirmed a role for CGRP in migraine pathophysiology and paved the way for therapeutic studies targeting this peptide as a novel treatment approach.

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This article will address the evidence behind the role of CGRP in migraine and the relevant anatomical distribution of its expression within the nervous system, possibilities for therapeutics development and then focus on pertinent research over the last 18 months which has led to exciting new drug discoveries, and an era which will likely bring these agents into our clinical practice and enhance the quality of lives of the migraine patients we look after.

**MEDIATION OF NOCICEPTION IN MIGRAINE**

Increasingly, evidence from animal studies and human functional imaging studies, has suggested the role of subcortical brain areas in mediation of nociception in migraine [14–16]. Whereas for a large part of the 20th Century the primary mechanism of pain in migraine was thought to be vasodilatation and with durovascular structures alone causing pain, it is now thought that subcortical structures and neurotransmitter effects outside of vasodilatation play the crucial role in migraine [17]. Importantly, transmission of nociceptive signalling to the brainstem and higher cortical structures involves CGRP, PACAP and nitric oxide synthase (NOS) [14].

Recently, Maniyar et al. [18] showed through PET imaging that during the premonitory symptoms of a migraine attack, before the onset of a headache, the hypothalamus and dorsolateral pons as well as the periaqueductal grey are activated. Such studies have supported that changes in vessels such as vasodilatation, which were historically thought to be the sole cause of the headache in migraine, are probably a later phenomenon in the entire migraine process and actually mediated secondary to diencephalic mechanisms and ascending nociceptive and descending inhibitory pathways [14].

**CALCITONIN GENE-RELATED PEPTIDE IN MIGRAINE**

CGRP is a potent vasodilator neuropeptide with long-lasting effects [19]. Early work in the 1980s by Edvinsson et al. [20] demonstrated that CGRP is present in the walls of intracranial vessels as well as cardiac vessels and is involved in mediating cranial vasodilatation. Immunohistochemistry also showed that CGRP is produced by cell bodies of ventral and dorsal root ganglia [21]. This led to studies exploring the role of CGRP and other neuropeptides in the primary headache disorders using animal studies, and later human studies, assessing neuropeptide release in response to trigeminovascular activation [8,22–24]. These showed that despite the expression of multiple neuropeptides within trigeminal neurons, only CGRP and PACAP are released during acute migraine. Both of these, if administered to humans, are capable of triggering migraine-like attacks [13,25].

Anatomically, within both the central nervous system and peripheral nervous system, CGRP often colocalizes with other neuropeptides, such as substance P in C-fibres [23,24]. It is dense in areas important to the migraine process, and particularly within areas of the trigeminovascular system, including the trigeminocervical complex (TCC), from which second order neurons activate ascending pathways to brain areas for sensory processing [26]. Fibres from pseudounipolar cell bodies in the trigeminal ganglion, along the blood–brain barrier, innervate intracranial structures. The central projection of these neurons is to the trigeminal nucleus caudalis and C1/C2 dorsal horn to form the TCC. CGRP is localized in the trigeminal ganglion and the ascending second order neurons and glia, and trigeminal nucleus caudalis stimulation causes peripheral CGRP release. The satellite glial cells of the trigeminal ganglion may have a role in modulating neuronal metabolism through gap junctions [27]. Projection areas from the TCC include the brainstem, thalamus and hypothalamus [28,29].

Brainstem stimulation causes trigeminovascular activation and peripheral CGRP release in addition to second and third order neuronal sensitization; mechanisms that probably contribute to allodynia, when the patient perceives nonpainful stimulation as painful [30,31]. Peripherally, CGRP is found in primary afferent sensory fibres and in fibres innervating virtually all vasculature within the body [32]. Taken together the data suggest that CGRP may therefore be involved in migraine mechanisms at both a central and peripheral level [33,34] and support the idea that migraineurs have a combination of altered sensory perception of non-noxious stimuli and altered brainstem and trigeminovascular activation, which
lead to a cycle of painful signalling and interpretation of nonpainful stimuli as painful.
CGRP has also been shown to have an important neuronal role outside of its neurovascular role in mediating neuronal plasticity and synapse formation; it is unclear if this is through direct glial actions, or via another modulatory pathway with other neuropeptides that it is often coexpressed with [35–37].

**CALCITONIN GENE-RELATED PEPTIDE AS A TREATMENT TARGET IN MIGRAINE**

As discussed, CGRP is widely located in the trigemino-vascular system, but is also expressed within the cerebellum, another anatomical site that is thought to be involved in modulation of cortical inputs and may have an inhibitory role in migraine with aura [38–40]. The cerebellum has been demonstrated on PET imaging studies to be activated during acute migraine attacks [41], and is also a particular area which is affected by stroke in migraine patients [42,43].

There is a clear localization of CGRP-containing neurons in anatomical areas within the nervous system, both within the trigeminovascular nociceptive system and outside of this, suggesting that CGRP may have a role in mediating some of the varied painful and non-painful symptomatology of migraine attacks. Additionally, CGRP-targeted therapies do not seem to have the coronary vasoconstricting side-effects that triptans do [44].

**CALCITONIN GENE-RELATED PEPTIDE-TARGETED DRUG THERAPIES**

CGRP mechanisms have been targeted either with small molecule receptor antagonists or most recently with monoclonal antibodies targeted at either the peptide or the receptor.

### The gepants

Six small molecule CGRP receptor antagonists have been developed and five of them have demonstrated clinical efficacy in acute migraine. This class of drugs has acquired the stem name the gepants.

A summary of these agents is detailed in Table 1 for clarity. Two compounds, telcagepant [46–52] and MK-3207 [53] have been discontinued due to hepatotoxic side-effects; olcegepant has been discontinued as an oral formulation was too difficult to develop [45], whereas two compounds BI44370A and BMS-927711 showed clinical efficacy in phase II studies [54,55]. MK-1602 has no reported data as yet [56,57].

### Monoclonal antibodies

The concept, that a monoclonal antibody could neutralize the effect of CGRP and therefore have clinical efficacy in migraine, has led to drug companies developing and testing humanized monoclonal antibodies to CGRP or its receptor. These have a long half-life and therefore require infrequent dosing, making them ideal in managing a chronic headache condition [58]. The gepants development seemed to overcome the problem of coronary vasculature side-effects that precludes triptan use in some patient groups. Unfortunately, hepatotoxicity inhibited further development of two of the agents despite their clear tolerability and clinical effect. These antibodies are generally renally excreted or excreted through the liver, without undergoing hepatic processing and they do not therefore cause hepatotoxicity [59–61], although there is no direct evidence even for the failed gepants that the liver effect was CGRP mechanism based. They do, however, carry the risks that come with the use of such biologic agents, including activation of latent tuberculosis and administration reactions, and given the long half-lives of these agents, these are not easy to reverse should they occur [60].

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**Table 1.** Note all data in this table, comparing verum to placebo, were statistically significant (\(P < 0.05\)) in the individual trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pain free at 2h (%)</th>
<th>Side-effects reported</th>
<th>Status in pharmacological trials</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olcegepant</td>
<td>Verum: 44; 2.5 mg</td>
<td>Placebo: 2</td>
<td>20% Reported adverse effects</td>
<td>Discontinued development – poor oral bioavailability [45]</td>
</tr>
<tr>
<td>Telcegepant</td>
<td>Verum: 27; 300 mg</td>
<td>Placebo: 10</td>
<td>Transaminits</td>
<td>Discontinued – hepatotoxic concerns [46–52]</td>
</tr>
<tr>
<td>MK3207</td>
<td>Verum: 69; 200 mg</td>
<td>Placebo: 39.1</td>
<td>Transaminits</td>
<td>Discontinued – hepatotoxic concerns [53]</td>
</tr>
<tr>
<td>BI44370</td>
<td>Verum: 27.4; 400 mg</td>
<td>Placebo: 8.6</td>
<td>1.4–9.4% Reported adverse effects, dose dependant</td>
<td>Phase IIa complete [54]</td>
</tr>
<tr>
<td>BMS-927711</td>
<td>Verum: 32.9; 150 mg</td>
<td>Placebo: 15.3</td>
<td>1–8% Reported adverse effects, dose dependant</td>
<td>Phase IIa complete [55]</td>
</tr>
</tbody>
</table>

Summary of the gepants class of calcitonin gene-related peptide antagonists that have demonstrated clinical efficacy and the recent literature from pharmacological studies regarding their effects and status in drug trials.
A number of anti-CGRP monoclonal antibodies have been researched in animals and are being researched in human studies. The ones to reach human studies and currently going through drug trials are summarized in Table 2. These agents are likely to make it into our clinical practice in the next few years and may have life-changing effects for patients suffering with migraine.

**CONCLUSION**

Years of research, both with animal and human headache models, has established a clear relationship between CGRP and migraine, and possibly cluster headache too [68]. CGRP is widely expressed within the nervous system, and particularly within the trigeminalvascular system and other sites such as the cerebellum and hypothalamus, which have through functional imaging studies been shown to be vital to the migraine process. CGRP is released with trigeminovascular activation, can induce migraine, and correlation of its blood levels with pain intensity has paved the way for CGRP to be investigated as a drug target for the primary headache disorders. Thus far every CGRP mechanism blocker studied in migraine has been effective. The potential to develop well tolerated therapies, that are mechanism-based and specifically developed for migraine, offers the prospect of a very substantial revolution in the management of this most disabling neurological malady.

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**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


