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CURRENT OPINION

# Targeting CGRP: A New Era for Migraine Treatment

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**Abstract** Migraine is a highly prevalent headache disease that typically affects patients during their most productive years. Despite significant progress in understanding the underlying pathophysiology of this disorder, its treatment so far continues to depend on drugs that, in their majority, were not specifically designed for this purpose. The neuropeptide calcitonin gene-related peptide (CGRP) has been indicated as playing a critical role in the central and peripheral pathways leading to a migraine attack. It is not surprising that drugs designed to specifically block its action are gaining remarkable attention from researchers in the field with, at least so far, a safe risk profile. In this article, we highlight the evolution from older traditional treatments to the innovative CGRP target drugs that are revolutionizing the way to approach this debilitating neurological disease. We provide a brief introduction on pathophysiology of migraine and details on the characteristic, function, and localization of CGRP to then focus on CGRP receptor antagonists (CGRP-RAs) and CGRP monoclonal antibodies (CGRP mAbs).

**Key Points**

The neuropeptide calcitonin gene-related peptide (CGRP) has been indicated as playing a critical role in the central and peripheral pathways leading to a migraine attack.

Targeting CGRP as a specific therapeutic tool for migraine may offer similar or even better efficacy than currently available treatments without the vasoconstrictive risk factors.

Further studies are necessary to determine the exact role of CGRP receptor antagonists and CGRP monoclonal antibodies in migraine with aura, allodynia, and photophobia.

## 1 Introduction

In the Global Burden of Disease Survey 2010, migraine was ranked as the third most prevalent disorder and seventh-highest specific cause of disability worldwide [1]. In the US population, approximately 8.7 million females and 2.6 million males experience migraine headache with moderate to severe disability [2]. Attacks are described as moderate to severe, usually with unilateral pulsatile pain, lasting 4–72 h and accompanied by nausea and/or vomiting, photophobia, and phonophobia [3]. The ergots, consisting of ergotamine and dihydroergotamine, are the oldest specific abortive anti-migraine drugs available, with ergotamine used less extensively because of its adverse effects [4].

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The treatment of this neurological condition had a major turning point in the early 1990s with the advance of serotonin 5-HT1B/1D receptor agonists, referred to as 'triptans', a class of medication to abort pain and many of the associated migraine symptoms [5]. Despite the significant contribution in the past quarter of a century, the overall associated cardiovascular risks continue to limit their use, and a significant amount of patients still may not respond to this approach [6]. Most especially, only about a third of patients treated with oral triptans will obtain sustained pain freedom (freedom from pain at 2 h with no rescue medication and with no recurrence of headache within 24 h), which supports the urgent need for novel therapy options [7].

When the frequency of attacks per month is significant, a variable range of drugs, such as beta-blockers, anticonvulsants, tricyclic antidepressants, and calcium channel blockers, have been studied for the purpose of prevention [8, 9]. The majority of preventive medications currently available was not designed for the treatment of migraine, and their use is often limited by an arsenal of side effects or inadequate relief [10–12]. In a study of 370 patients attending a headache clinic in a tertiary center, 5.1 % were found to have refractory migraine defined by failure of at least two of the four drug classes previously mentioned [13]. Although it is difficult to determine the exact number of patients who are refractory to conventional treatment, such patients are not rare and represent a wake-up call for the development of new compounds in migraine therapy [14].

Targeting of calcitonin-gene-related peptide (CGRP) as a specific therapeutic tool has emerged due to the urgent need to provide pain relief and to assimilate migraine sufferers back into society.

This review aims to familiarize the reader with current literature regarding CGRP and how it has been targeted to improve the treatment of migraine headaches. We hope to point out the advantages of this approach, address unanswered questions about this subject, and highlight future directions.

## 2 Pathophysiology

Migraine is not a primary vascular but rather a neurovascular disorder in which neural events lead to pain and further nerve activation [7]. The trigeminal nerve, mostly its first division (ophthalmic nerve $V_1$), is responsible for the majority of afferent pain information from structures above the tentorium cerebelli. Unmyelinated C fibers that innervate those pain-sensitive structures store several neuropeptides, including substance P, CGRP, and neurokinin A, passing through the trigeminal ganglion to enter the pons and reach the trigeminal nucleus caudalis (TNC) [15]. The TNC extends caudally to connect with the first three cervical segments of the spinal cord and rostrally sends fibers to the thalamus, autonomic nucleus in the pons (superior salivatory nucleus [SSN]), and hypothalamus. The SSN, in turn, activates postganglionic parasympathetic neurons in the sphenopalatine ganglion, resulting in vasodilation and local release of inflammatory molecules that activate meningeal nociceptors [16]. This pathway, often referred to as trigeminocervical complex, has been studied extensively in animal models by Goadsby and colleagues [17–19].

The exact mechanism by which a migraine attack is initiated is still poorly understood, but it is now well accepted that brain dysfunction involving peripheral and central components of the trigeminovascular system leads to the release of inflammatory mediators that ultimately result in propagation and perpetuation of pain [20].

Attention to the peripheral component is important to understand that an anti-migraine drug may not need to penetrate the blood–brain barrier (BBB) or reach the central nervous system (CNS) to be effective [21]. Elevated levels of CGRP, but not of other neuropeptides, were found in the external jugular vein during the headache phase of migraine and normalized in parallel with headache improvement [22, 23]. Furthermore, infusion of human CGRP was found to trigger a migraine attack in susceptible individuals, while normalization of CGRP levels were obtained after migraine treatment with triptans [24–26]. These findings provided new insight into a putative role of CGRP in the pathophysiology of migraine, opening new pathways for therapeutic intervention.

### 2.1 The Molecule

CGRP, a potent vasodilator, is a 37-amino acid neuropeptide member of the calcitonin family of peptides first identified in 1983 [27]. The calcitonin family of peptides comprises calcitonin, amylin, two CGRPs, and adrenomedullin [28]. The original function of CGRP was thought to be the maintenance of vascular homeostasis, although it has been speculated that throughout evolution it acquired a new and more important role of nociceptive transmission [29].

CGRP exists in two forms, α-CGRP and β-CGRP. α-CGRP is the main form expressed in trigeminal ganglia neurons resulting from the alternative splicing of the calcitonin/CGRP gene located on chromosome 11 [30]. It contains an N-terminal disulfide bridge, an α-helix, either a β or a γ-turn and a phenylalanyl amide C-terminus [31]. The less-studied and understood β-CGRP differs in three amino acids in humans; is encoded in a separate gene; and is primarily found in intrinsic enteric neurons and the pituitary gland [20, 32, 33]. It is possibly involved in

gastroparesis and other gastrointestinal problems often associated with migraine [34]. The focus of this paper will be on α-CGRP, here referred to simply as CGRP.

### 2.2 Localization

Predominately expressed in C and A delta nociceptive nerve fibers, CGRP is widely distributed in the central and peripheral nervous system as described by van Rossum et al. [33] and it does not readily cross the BBB [35]. CGRP may work at the intersection between the peripheral and central components of migraine [36]. In the periphery, CGRP is abundantly present in dorsal horn cells co-stored with substance P in primary sensory ganglia, and with acetylcholine in motor neurons [37, 38]. In the CNS, CGRP is involved in modulating pain transmission [39]. Kawai et al. [40] and Skofitsch and Jacobowitz [41] demonstrated the presence of CGRP-positive cell bodies in the preoptic area and hypothalamus, ventromedial thalamus, medial amygdala, hippocampus, superior colliculus, lateral lemniscus, and dentate gyrus and in Purkinje cells of the cerebellum [42]. The highest densities of neurons expressing the CGRP messenger RNA (mRNA) have been observed in all cranial nuclei with the exception of the dorsal motor nucleus of the vagus nerve (X) [33].

The localization of CGRP and its receptor, particularly related to migraine pathophysiology, has been substantially investigated by Eftekhari et al. [43]. CGRP and CGRP receptor components showed immunoreactivity in different neurons and separate fibers in rhesus monkey trigeminal ganglion [43] and in dura mater of rats [44]. CGRP was expressed in thin, unmyelinated branched nerve fibers while receptor components were found in thicker myelinated fibers and vessel walls. CGRP and its receptor components were also found in different locations, respectively, within the TNC and C1-level of the spinal cord of man and rat [45]. This suggests that the CGRP production site is different than where the peptide normally acts. Furthermore, once released from C- and A-delta fibers, CGRP most likely acts post-junctionally to modulate activity in separate fibers where the receptors are located.

CGRP seems to be the most prominent peptide in animal dura mater and trigeminal ganglia when compared with other nerve markers such as substance P, vasoactive intestinal peptide (VIP), neuronal nitric oxide synthase (nNOS), and pituitary adenylate cyclase-activating polypeptide (PACAP). Receptor components have also been found in the dural mast cells of rats, suggesting a putative role in mast cell degranulation and inflammation, although these findings have not yet been reproduced in humans [44, 45].

### 2.3 Function

The exact functional role of CGRP in various systems in the body is still under investigation. It is known that this peptide exerts a wide variety of biological effects on various tissues, including the cardiovascular, smooth, and skeletal muscles, and endocrine and gastrointestinal systems through activation of specific plasma membrane receptor sites [38, 46, 47]. It is extremely important to be aware of these systemic contributions, since the administration of antagonists can affect CGRP function outside the nervous system.

In the CNS, CGRP is involved in pain modulation, perception, and central sensitization [48]. It potentiates the release of substance P from primary afferent terminals and promotes nociceptive information transmission induced by noxious stimuli [49]. CGRP is also implicated in modulating synaptic transmission of glutamate and acetylcholine [50–52]. In the periphery, release of CGRP from trigeminal fibers is believed to cause vasodilation and mast cell degranulation, ultimately resulting in a persistent pro-inflammatory sensitization of trigeminal nociceptors [53–55]. Studies have suggested that CGRP release works in a paracrine manner, causing excitation of nearby neuronal and satellite glial cells and stimulating its own synthesis [56]. This cascade of events supports the role of CGRP in the development and maintenance of peripheral and central sensitization in migraine pathogenesis [20]. Furthermore, animal studies demonstrated that CGRP plays a key role in light-aversive behavior, a common and often debilitating feature of migraine. Transgenic mice overexpressing CGRP receptors spent significantly less time in the light than did controls [57].

### 2.4 The Receptor

CGRP receptors belong to the G protein-coupled receptor superfamily and were initially classified into two major subtypes, namely the CGRP1 and the CGRP2. A third subtype with different pharmacological properties has also been proposed [33]. Recent data suggest that CGRP2 functions as amylin and adrenomedullin receptors and for this purpose should not be referred to as a 'CGRP' receptor [58].

First cloned in 1991, the CGRP receptor is composed of a G protein-coupled receptor known as the calcitonin-like receptor (CLR), a receptor component protein (RCP) that defines the G protein to which the receptor couples, and a single transmembrane domain protein called receptor activity-modifying protein 1 type (RAMP1) [28, 59]. CGRP receptor stimulation results in activation of the cyclic adenosine monophosphate (cAMP)-signaling pathway [60]. The neuropeptide C-terminal residues bind to a

cleft at the interface of CLR and RAMP1, followed by the binding of N-terminal CGRP residues to the juxtamembrane domain, leading to receptor activation [28]. Small-molecule antagonists discussed below act by blocking the binding to the peptide-binding cleft [61]. RAMP1 is involved in processing and presenting the CGRP receptor to the cell surface and helps determine the relative affinity and sensitivity of the receptor [62, 63]. Zhang et al. [64] showed that RAMP1 is functionally rate limiting for CGRP receptor activity in the trigeminal ganglion, suggesting that elevated RAMP1 could sensitize migraine sufferers to CGRP actions [64]. RAMP2 and -3 enable adrenomedullin receptor function, while the amylin receptor is formed by the calcitonin receptor (CTR) and RAMP1 [28]. Despite the distribution of adrenomedullin and amylin receptors within the trigeminovascular system, they are not thought to play a major role in the pathophysiology of migraine. Injection of adrenomedullin, unlike CGRP, failed to induce a migraine attack [65, 66].

Using immunostaining technique, Walker et al. [67] were able to isolate different receptor components from rat TG neurons and consequently differentiate the CGRP receptor, formed by a CLR/RAMP1 combination, from an amylin receptor (AMY1), formed by CTR/RAMP1 [67]. The complex CTR/RAMP1 is classified as an amylin receptor, which explains the name AMY1, but has also a high affinity for CGRP and consequently is considered a dual CGRP/amylin receptor [68, 69]. Both receptors, CGRP and AMY1, are strongly and equally represented in rat TG neurons since equipotent results are found when antagonizing each of them separately. Data also suggest the presence of AMY1 receptors in human TG and brainstem, more specifically in the TNC. The exact role of AMY1 in migraine has yet to be defined, but the distribution of this newly identified receptor within areas of the brain linked to migraine pathophysiology may offer a viable target for the treatment of this disorder. More importantly, dual CGRP/AMY1 antagonists may have greater efficacy than isolated CGRP and AMY1 antagonists [70].

### *2.4.1 CGRP Receptor Antagonists*

Doods et al. [71] described the first potent and selective non-peptide human CGRP-receptor antagonist (RA): BIBN4096BS, later renamed olcegepant. Prior to that, N-terminal-truncated CGRP fragments have been described as antagonists, but with limited use in vivo because of their short half-life, lower affinity, and non-selectiveness [20, 72]. Intravenous doses of olcegepant of between 1 and 30 μg/kg inhibited increase in facial skin blood flow induced by CGRP in marmoset monkeys. According to the authors, no intrinsic cardiovascular effects were reported. The affinity of olcegepant for the CGRP receptor was RAMP1 related, directly competing with CGRP for its binding site [73]. In 2004, Olesen et al. [74] reported the positive outcomes of CGRP-RA as a migraine-abortive therapy with similar effectiveness to that of oral sumatriptan. A dose of 2.5 mg was considered to be ideal, with a response rate of 66 % as compared with 27 % for placebo ($p = 0.001$). The lack of cardiovascular side effects, such as changes in basal blood pressure or heart rate, was thought to be promising, but its intravenous administration and difficulties with developing an oral formulation limited routine use [74, 75].

In 2006, Merck Research Laboratories formulated MK-0974, a highly selective oral antagonist of the human CGRP receptor, later renamed telcagepant [76, 77]. In a randomized, double-blind clinical trial, doses of telcagepant ranging from 300 to 600 mg were found to be as effective as oral rizatriptan 10 mg and superior to placebo in the treatment of a moderate or severe migraine attack. Based on both the primary endpoint of pain relief at 2 h and secondary endpoints of pain freedom at 2 h and sustained pain relief at 24 h, the oral CGRP antagonist was more efficacious than placebo. The study was also helpful to guide dose selection for future clinical trials, since lower doses of telcagepant at 25, 50, 100, and 200 mg were found to have insufficient efficacy. Further studies indicated that triptan non-responders would still benefit from the CGRP-RA [78]. Telcagepant was well tolerated, with the most common adverse effects being nausea, dizziness, and somnolence, similar among treatment groups and placebo [79]. In a randomized controlled trial, therapeutic effects of telcagepant 300 mg were identical to those of zolmitriptan 5 mg in the acute treatment of migraine, with fewer associated adverse effects. Treatment of photophobia, phonophobia, and nausea was also found to be superior to placebo [80]. Cardiovascular safety has also been demonstrated with adequate tolerability in patients with comorbid stable coronary artery disease [81]. The blocking of CGRP effects is believed to restore vascular tone rather than causing vasoconstriction [82].

Ho et al. [83] investigated the role of telcagepant in migraine prevention. Patients experiencing fewer than 15 migraine days per month were randomized to receive telcagepant 140 mg, telcagepant 280 mg, or placebo twice daily for 12 weeks. Authors found that daily doses of telcagepant reduced headache days by 1.4 days per month compared with placebo. Unfortunately, the study was terminated after findings of liver toxicity among the treated group, with 2 % of patients showing elevated alanine aminotransferase (ALT) and 1 % showing abnormal levels of both ALT and aspartate aminotransferase (AST) [83].

At least eight distinct CGRP-RAs have been identified, six of them being clinically tested: olcegepant (BIBN4096BS), telcagepant (MK-0974), MK-3207, BI

44370 TA, BMS-927711, MK-1602 [34]. Despite evidence of therapeutic effects and tolerability of these small molecules in phase I, II, and—for telcagepant—phase III clinical trials, findings of elevated transaminases in a small number of patients taking daily telcagepant precluded its use [84, 85]. At this point, only one CGRP-RA, BI 44370 TA, is under investigation. Results from the phase II trial showed that BI 44370 TA 400 mg was similar to eletriptan 40 mg and superior to placebo in the acute treatment of migraine. Studied patients included those who experienced episodic migraine with and without aura and excluded those overusing other abortive medications [86].

CGRP-RAs were initially formulated for the acute management of a migraine attack. Although signs of liver toxicity were only observed with chronic continuous administration, it could not be disregarded, especially since migraine patients often overuse abortive treatments, taking them daily instead of sporadically. These findings generated interest in compounds that would bypass the liver metabolism. Monoclonal antibodies (mAbs) against the CGRP ligand and CGRP receptor became an alternative approach, avoiding many of the issues seen with CGRP-RAs [75].

#### *2.4.2 CGRP Monoclonal Antibodies (mAbs)*

mAbs are macromolecules made of proteins that are incapable of crossing the BBB unless engineered to do so [87]. Preferably, they are delivered through intravenous, subcutaneous, or intramuscular routes since their large size and hydrophilicity make oral absorption difficult [88].

Antibody therapy dates back to the nineteenth century, when immunized animal sera were used to treat diseases such as diphtheria and tetanus [89]. The first mAb, muromonab-CD3, was approved in 1986 and since then our knowledge of immunogenicity has significantly expanded with a broad range of clinical applicability [90]. Four fully humanized mAbs are in different stages of phase I and II clinical trial investigation for the treatment of migraine. Three are targeting the CGRP ligand: LY2951742 (developed by Eli Lilly and Co.); ALD-403 (developed by Alder Biopharmaceuticals); and TEV-48125 (LBR-101) (developed by Teva Pharmaceuticals); and one against its receptor, AMG 334 (in development by Amgen). The two main administration routes are intravenous or subcutaneous. Both episodic and chronic migraine patients are being targeted in all four studies. The mAbs against the ligand are thought to remove excessive CGRP that is released at perivascular trigeminal sensory nerve fibers, while the receptor mAbs block CGRP signaling [10].

Preliminary data showed positive results for all four mAbs. Subcutaneous LY2951742 150 mg for patients with episodic migraine was superior to placebo and generally well tolerated for migraine prevention [91]. Intravenous ALD403 1000 mg was also found to be safe, well tolerated, and more efficacious than placebo in the prevention of migraine in patients with episodic migraine. ALD403 has a rapid onset of action, and 26 % of patients had no migraines in the first month following a single intravenous dose of 1000 mg, which also provided lasting efficacy to 6 months [92]. Most adverse events, including upper respiratory and urinary tract infection, fatigue, back pain, nausea/vomiting, and arthralgia were transient and deemed to be unrelated to study drug [93].

Results from a multi-dose study comparing the efficacy and safety of subcutaneous TEV-48125 with that of placebo for the preventive treatment of chronic migraine support continued clinical development in a phase III trial. TEV-48125 was associated with significant decrease in the use of acute migraine medication, and no safety concerns have emerged [94].

AMG 334 was evaluated in 242 subjects in a phase I study at subcutaneous doses up to 280 mg and intravenous doses of 140 mg. A statistically significant reduction in monthly headache days and migraine-specific medication use days were observed at week 12 with doses of 70 mg [95].

Small molecules, such as CGRP-RAs, have the advantage of formulation flexibility, including oral delivery, which is crucial in terms of access, patient preference, healthcare costs, and therapeutic safety margin [79]. On the other hand, mAbs are target specific, which limits off-target toxicities common to all small molecules. Its longevity allows less frequent administration of once a month or even less compared with the usual daily dosing of small molecules, though once discontinued, the clearance is not immediate [10]. Their long half-life also explains why these molecules are under investigation for migraine prevention rather than as abortives.

CGRP is a vasodilator peptide. Thus, antagonizing its effects raises concerns with possible cardiovascular risks such as medication-induced hypertension and inhibition of cardio-protective mechanisms during ischemia [96]. Two independent studies in monkeys found no electrocardiogram or hemodynamic changes from long-term inhibition of CGRP with LBR-101 [97, 98]. The drug was well tolerated and, thus far, no relevant cardiovascular effects have been reported [10]. CGRP antibodies inhibited skin vasodilatation in rats, still evident 1 week after dosing. No effects on animal heart rate or blood pressure were detected; this is consistent with CGRP primarily being a compensatory peptide with modulatory roles in the body [34, 99]. Side effects from a broad range of dosages (0.2–2000 mg) of intravenous LBR-101 were reported to be mostly mild, with one serious adverse event of 'thoracic aortic aneurysm' in a participant who was later diagnosed with Ehlers-Danlos syndrome. No laboratory abnormalities were reported, including liver toxicity. A case of glaucoma

in a 64-year-old patient almost 3 months after a single exposure was considered non-related [100]. Concerns regarding the consequences on various tissues other than the nervous system of antagonizing or inhibiting CGRP effects have not emerged, and, so far, studies have shown an overall reassuring safety profile [101].

Immune response against the therapeutic protein is common and even expected with the production of neutralizing antibodies that may unfortunately lead to drug ineffectiveness. Immune incompatibility usually associated with major systemic consequences are concerning, although rare, given the development of fully humanized antibodies that minimize the immunologic liability [100].

## 3 Blood–Brain Barrier

Controversy exists about whether CGRP-RAs penetrate the BBB and whether that would be relevant to their mode of action [75, 93]. Measures of CGRP-RA cerebrospinal fluid (CSF) levels in rhesus monkeys demonstrate that these molecules can penetrate the brain even in small quantities. The CSF/plasma ratio in primates for telcagepant, for example, was found to be about 1.4 % [102]. Despite these findings, low central receptor occupancy after efficacious dose (140 mg orally) of telcagepant suggests that this is not the responsible mechanism for its clinical efficacy [103]. A recent study found high-binding densities of the CGRP-RA MK-3207 in the trigeminal ganglion of rhesus monkeys, which is located outside of the BBB. [43]. Positron emission tomography (PET) imaging studies in healthy subjects and migraineurs demonstrated that CGRP-RAs do not act centrally [104]. Similarly, intravenous administration of CGRP can induce migraine in susceptible individuals without crossing the BBB [24]. Antibodies consist of larger size molecules that are even less likely to cross the BBB. Recent positive clinical trials with two CGRP mAbs, LY2951742 and ALD403, indicate that efficacy can be achieved via actions at the periphery alone [91, 93]. Thus, modulation of CGRP and migraine management may happen outside of the CNS, with the meninges and trigeminal ganglion described as potential sites of action [105]. Overall, this subject still requires continuous investigation, as some may suggest that the BBB is disrupted during a migraine attack [106] and following cortical spreading depression [107].

## 4 Migraine and Aura

Aura is defined as the complex of neurological symptoms that occurs, usually but not always, before the pain phase of migraine [3]. Cortical spreading depression is the electrophysiological manifestation of aura in the cerebral cortex thought to activate the trigeminovascular system and ultimately provoke headache. Controversy exists as to whether this process happens through CGRP release from peripheral trigeminal terminals [34, 108, 109]. Studies in rats showed endogenous release of CGRP during extracellular hyperkalemia-induced cortical spreading depression and inhibition of this phenomena by CGRP-RAs [110]. Meanwhile, cortical spreading depression did not increase CGRP levels in the external jugular veins of cats [111].

The fact that CGRP can induce an attack in both migraine phenotype spectrum, i.e. without aura (MO) and with aura (MA), suggests a common basic pathophysiology mechanism between them [25]. Further studies are necessary to clarify whether individuals affected by migraine with aura respond differently to CGRP target treatments when compared with those without.

## 5 Migraine and Allodynia

Overuse of abortive medications such as opioids and triptans induces neural adaptations that result in a state of permanent sensitization, even after the drug is discontinued [112]. This persistent state of excitability is clinically perceived as hyperalgesia and allodynia. CGRP is thought to play an important role in these neuroadaptive changes, including increase in its expression at the trigeminal primary afferent neurons [113]. Olcegepant significantly reduced mechanical allodynia induced by infraorbital nerve ligation in animal models [114]. Similarly, another CGRP-RA ($\alpha$-$CGRP_{8-37}$) produced reversal of periorbital and hind paw sensitivity to light tactile stimuli [112].

## 6 Migraine and Photophobia

About seven out of ten migraineurs with intact eyesight have abnormal sensitivity to light and exacerbation of migraine headache by light, termed photophobia and photo-oculodynia, respectively [115, 116]. This subject has been extensively studied by Noseda, Maleki and Burstein, who proposed a non-imaging pathway involving melanopsin-containing photosensitive retinal ganglion cells and the posterior thalamus [117, 118]. As previously mentioned, the role of CGRP in light-aversive behavior has been demonstrated by animal models, and photophobia has been shown to improve with CGRP target treatment. Further studies are necessary, and data should be carefully interpreted since CGRP is unlikely to be the single culprit in this phenomenon.

## 7 Conclusions

We have entered a new era for the treatment of migraine that marks the evolution from ergotamines and triptans to new compounds that may offer similar or even better efficacy without the vasoconstrictive risk factors caused by previous ones. Acknowledging the complexity of migraine as a neurological disorder, CGRP cannot be indicated as uniquely responsible for its genesis. That being said, studies continue to point to this peptide as a major contributor. The development of CGRP-RAs and mAbs represent the power of translational research, when years spent in understanding the pathophysiology of migraine can now be applied in the development of a target-specific medication for such a debilitating condition. Many questions are still to be answered: Is there a subset of migraineurs who will respond better to this treatment and, if yes, how can we identify them? Can aura be treated separately? Given the important role of CGRP in nociceptive transmission and modulation, will we be able to treat other painful conditions when antagonizing its action? If mAbs prove to be well tolerated and efficacious in human models, will we be able to offer an oral formulation to facilitate self-administration and compliance? As with everything in science, the unanswered questions will continue to move us forward with at least one certainty: that we seem to be heading in the right direction.

**Compliance with ethical standards**

**Conflict of interest** Dr. Goldberg has received honoraria from MedLink Corporation for reviewing different topics on neurological disorders. As a consultant and/or advisory panel member, Dr. Silberstein receives honoraria from Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; Depomed; Dr. Reddy's Laboratories; eNeura Inc.; ElectroCore Medical, LLC; Ipsen Biopharmaceuticals; Medscape, LLC; Medtronic, Inc; Mitsubishi Tanabe Pharma America, Inc.; NINDS; St. Jude Medical; Supernus Pharmaceuticals, Inc; Teva Pharmaceuticals, and Trigemina, Inc.

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## References

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2197–223.
2. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race and other sociodemographic factors. JAMA. 1992;267:64–9.
3. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808.
4. Monteith TS, Goadsby PJ. Acute migraine therapy: new drugs and new approaches. Curr Treat Options Neurol. 2011;13:1–14.
5. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. Headache. 2003;43:729–33.
6. Papademetriou V. Cardiovascular risk assessment and triptans. Headache. 2004;44(Suppl 1):S31–9.
7. Goadsby PJ, Lipton RB, Ferrari MD. Migraine-current understanding and treatment. N Engl J Med. 2002;346:257–70.
8. Rizzoli P. Preventive pharmacotherapy in migraine. Headache. 2014;54:364–9.
9. Goadsby PJ. Therapeutic prospects for migraine: can paradise be regained? Ann Neurol. 2013;74:423–34.
10. Bigal ME, Walter S, Rapoport AM. Therapeutic antibodies against CGRP or its receptor. Br J Clin Pharmacol. 2015;79:886–95.
11. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78:1337–45.
12. Martelletti P. The therapeutic armamentarium in migraine is quite elderly. Expert Opin Drug Metab Toxicol. 2015;11:175–7.
13. Irimia P, Palma JA, Fernandez-Torron R, Martinez-Vila E. Refractory migraine in a headache clinic population. BMC Neurol. 2011;11:94.
14. Goadsby PJ, Silberstein SD, Dodick DW. Chronic daily headaches for clinicians. Hamilton: BC Decker Inc; 2005.
15. Edvinsson L. Blockade of CGRP receptors in the intracranial vasculature: a new target in the treatment of headache. Cephalalgia. 2004;24:611–22.
16. Burstein R, Jakubowski M. Unitary hypothesis for multiple triggers of the pain and strain of migraine. J Comp Neurol. 2005;493:9–14.
17. Goadsby PJ, Zagami AS. Stimulation of the superior sagittal sinus increases metabolic activity and blood flow in certain regions of the brainstem and upper cervical spinal cord of the cat. Brain. 1991;114:1001–11.
18. Goadsby PJ, Zagami AS, Lambert GA. Neural processing of craniovascular pain: synthesis of the central structures involved in migraine. Headache. 1991;31:365–71.
19. Goadsby PJ, Hoskin KL, Knight YE. Stimulation of the greater occipital nerve increases metabolic activity in the trigeminal nucleus caudalis and cervical dorsal horn of the cat. Pain. 1997;73:23–8.
20. Durham PL, Vause CV. Calcitonin gene-related peptide (CGRP) receptor antagonists in the treatment of migraine. CNS Drugs. 2010;24:539–48.
21. Bigal ME, Walter S, Rapoport AM. The vasodilatory activity of CGRP: a response. Headache. 2014;54:748–9.
22. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol. 1990;28:183–7.
23. Arulmani U, MaassenVanDenBrink A, Villalon CM, Saxena PR. Calcitonin gene-related peptide and its role in migraine pathophysiology. Eur J Pharmacol. 2004;500:315–30.
24. Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. Cephalalgia. 2002;22:54–61.
25. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia. 2010;30:1179–86.
26. Cady RK, Vause CV, Ho TW, Bigal ME, Durham PL. Elevated saliva calcitonin gene-related peptide levels during acute migraine predict therapeutic response to rizatriptan. Headache. 2009;49:1258–66.
27. Rosenfeld MG, Mermod JJ, Amara SG, et al. Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing. Nature. 1983;304:129–35.

28. Poyner DR, Sexton PM, Marshall I, et al. International union of pharmacology. XXXII. The mammalian calcitonin gene-related peptides, adrenomedullin, amylin, and calcitonin receptors. Pharmacol Rev. 2002;54:233–46.
29. Lafont AG, Dufour S, Fouchereau-Peron M. Evolution of the CT/CGRP family: comparative study with new data from models of teleosts, the eel, and cephalopod molluscs, the cuttlefish and the nautilus. Gen Comp Endocrinol. 2007;153:155–69.
30. Rezaeian AH, Isokane T, Nishibori M, et al. alphaCGRP and betaCGRP transcript amount in mouse tissues of various developmental stages and their tissue expression sites. Brain Dev. 2009;31:682–93.
31. Conner AC, Hay DL, Howitt SG, et al. Interaction of calcitonin-gene-related peptide with its receptors. Biochem Soc Trans. 2002;30:451–5.
32. Sternini C. Enteric and visceral afferent CGRP neurons. Targets of innervation and differential expression patterns. Ann N Y Acad Sci. 1992;657:170–86.
33. van Rossum D, Hanisch UK, Quirion R. Neuroanatomical localization, pharmacological characterization and functions of CGRP, related peptides and their receptors. Neurosci Biobehav Rev. 1997;21:649–78.
34. Russo AF. Calcitonin gene-related peptide (CGRP): a new target for migraine. Annu Rev Pharmacol Toxicol. 2015;55:533–52.
35. Edvinsson L, Nilsson E, Jansen-Olesen I. Inhibitory effect of BIBN4096BS, CGRP(8-37), a CGRP antibody and an RNA-Spiegelmer on CGRP induced vasodilatation in the perfused and non-perfused rat middle cerebral artery. Br J Pharmacol. 2007;150:633–40.
36. Raddant AC, Russo AF. Calcitonin gene-related peptide in migraine: intersection of peripheral inflammation and central modulation. Expert Rev Mol Med. 2011;13:e36.
37. Tschopp FA, Henke H, Petermann JB, et al. Calcitonin gene-related peptide and its binding sites in the human central nervous system and pituitary. Proc Natl Acad Sci USA. 1985;82:248–52.
38. Wimalawansa SJ. Calcitonin gene-related peptide and its receptors: molecular genetics, physiology, pathophysiology, and therapeutic potentials. Endocr Rev. 1996;17:533–85.
39. Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. Nat Rev Neurol. 2010;6:573–82.
40. Kawai Y, Takami K, Shiosaka S, et al. Topographic localization of calcitonin gene-related peptide in the rat brain: an immunohistochemical analysis. Neuroscience. 1985;15:747–63.
41. Skofitsch G, Jacobowitz DM. Quantitative distribution of calcitonin gene-related peptide in the rat central nervous system. Peptides. 1985;6:1069–73.
42. Eftekhari S, Salvatore CA, Gaspar RC, et al. Localization of CGRP receptor components, CGRP, and receptor binding sites in human and rhesus cerebellar cortex. Cerebellum. 2013;12:937–49.
43. Eftekhari S, Salvatore CA, Johansson S, Chen TB, Zeng Z, Edvinsson L. Localization of CGRP, CGRP receptor, PACAP and glutamate in trigeminal ganglion. Relation to the blood-brain barrier. Brain Res. 2015;1600:93–109.
44. Eftekhari S, Warfvinge K, Blixt FW, Edvinsson L. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. J Pain. 2013;14:1289–303.
45. Eftekhari S, Edvinsson L. Calcitonin gene-related peptide (CGRP) and its receptor components in human and rat spinal trigeminal nucleus and spinal cord at C1-level. BMC Neurosci. 2011;12:112.
46. Goodman EC, Iversen LL. Calcitonin gene-related peptide: novel neuropeptide. Life Sci. 1986;38:2169–78.
47. Yallampalli C, Chauhan M, Thota CS, Kondapaka S, Wimalawansa SJ. Calcitonin gene-related peptide in pregnancy and its emerging receptor heterogeneity. Trends Endocrinol Metab. 2002;13:263–9.
48. Powell KJ, Ma W, Sutak M, Doods H, Quirion R, Jhamandas K. Blockade and reversal of spinal morphine tolerance by peptide and non-peptide calcitonin gene-related peptide receptor antagonists. Br J Pharmacol. 2000;131:875–84.
49. Oku R, Satoh M, Fujii N, Otaka A, Yajima H, Takagi H. Calcitonin gene-related peptide promotes mechanical nociception by potentiating release of substance P from the spinal dorsal horn in rats. Brain Res. 1987;403:350–4.
50. Marvizon JC, Perez OA, Song B, et al. Calcitonin receptor-like receptor and receptor activity modifying protein 1 in the rat dorsal horn: localization in glutamatergic presynaptic terminals containing opioids and adrenergic alpha2C receptors. Neuroscience. 2007;148:250–65.
51. Seybold VS. The role of peptides in central sensitization. Handb Exp Pharmacol 2009;194:451–91.
52. Rossi SG, Dickerson IM, Rotundo RL. Localization of the calcitonin gene-related peptide receptor complex at the vertebrate neuromuscular junction and its role in regulating acetylcholinesterase expression. J Biol Chem. 2003;278:24994–5000.
53. Ottosson A, Edvinsson L. Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide. Cephalalgia. 1997;17:166–74.
54. Messlinger K, Hanesch U, Kurosawa M, Pawlak M, Schmidt RF. Calcitonin gene related peptide released from dural nerve fibers mediates increase of meningeal blood flow in the rat. Can J Physiol Pharmacol. 1995;73:1020–4.
55. Strassman AM, Raymond SA, Burstein R. Sensitization of meningeal sensory neurons and the origin of headaches. Nature. 1996;384:560–4.
56. Thalakoti S, Patil VV, Damodaram S, et al. Neuron-glia signaling in trigeminal ganglion: implications for migraine pathology. Headache. 2007;47:1008–23.
57. Recober A, Kuburas A, Zhang Z, Wemmie JA, Anderson MG, Russo AF. Role of calcitonin gene-related peptide in light-aversive behavior: implications for migraine. J Neurosci. 2009;29:8798–804.
58. Hay DL, Poyner DR, Quirion R. International Union of Pharmacology. LXIX. Status of the calcitonin gene-related peptide subtype 2 receptor. Pharmacol Rev. 2008;60:143–5.
59. Lin HY, Harris TL, Flannery MS, et al. Expression cloning of an adenylate cyclase-coupled calcitonin receptor. Science. 1991;254:1022–4.
60. Walker CS, Conner AC, Poyner DR, Hay DL. Regulation of signal transduction by calcitonin gene-related peptide receptors. Trends Pharmacol Sci. 2010;31:476–83.
61. ter Haar E, Koth CM, Abdul-Manan N, et al. Crystal structure of the ectodomain complex of the CGRP receptor, a class-B GPCR, reveals the site of drug antagonism. Structure. 2010;18:1083–93.
62. Kusano S, Kukimoto-Niino M, Akasaka R, et al. Crystal structure of the human receptor activity-modifying protein 1 extracellular domain. Protein Sci. 2008;17:1907–14.
63. Foord SM, Marshall FH. RAMPs: accessory proteins for seven transmembrane domain receptors. Trends Pharmacol Sci. 1999;20:184–7.
64. Zhang Z, Winborn CS, de Marquez PB, Russo AF. Sensitization of calcitonin gene-related peptide receptors by receptor activity-modifying protein-1 in the trigeminal ganglion. J Neurosci. 2007;27:2693–703.
65. Walker CS, Hay DL. CGRP in the trigeminovascular system: a role for CGRP, adrenomedullin and amylin receptors? Br J Pharmacol. 2013;170:1293–307.
66. Petersen KA, Birk S, Kitamura K, Olesen J. Effect of adrenomedullin on the cerebral circulation: relevance to primary headache disorders. Cephalalgia. 2009;29:23–30.

67. Walker CS, Eftekhari S, Bower RL, et al. A second trigeminal CGRP receptor; function and expression of the $AMY_1$ receptor. Ann Clin Translational Neurol. 2015. doi:10.1002/acn3.197.
68. Bailey RJ, Walker CS, Ferner AH, et al. Pharmacological characterization of rat amylin receptors: implications for the identification of amylin receptor subtypes. Br J Pharmacol. 2012;166:151–67.
69. Hay DL, Christopoulos G, Christopoulos A, Poyner DR, Sexton PM. Pharmacological discrimination of calcitonin receptor: receptor activity-modifying protein complexes. Mol Pharmacol. 2005;67:1655–65.
70. Hay DL, Eftekhari S, Bower RL, Wilderman A, Insel PA, Edvinsson L, Waldvogel HJ, Russo AF, Caron KM, and Walker CS Function and expression of two calcitonin gene-related peptide receptors within the sensory trigeminal system. In: 17th Congress of the International Headache Society, Valencia, 2015.
71. Doods H, Hallermayer G, Wu D, et al. Pharmacological profile of BIBN-4096BS, the first selective small molecule CGRP antagonist. Br J Pharmacol. 2000;129:420–3.
72. Chiba T, Yamaguchi A, Yamatani T, et al. Calcitonin gene-related peptide receptor antagonist human CGRP-(8-37). Am J Physiol. 1989;256:E331–5.
73. Mallee JJ, Salvatore CA, LeBourdelles B, et al. Receptor activity-modifying protein 1 determines the species selectivity of non-peptide CGRP receptor antagonists. J Biol Chem. 2002;277:14294–8.
74. Olesen J, Diener HC, Husstedt IW, et al. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med. 2004;350:1104–10.
75. Bigal ME, Walter S. Monoclonal antibodies for migraine: preventing calcitonin gene-related peptide activity. CNS Drugs. 2014;28:389–99.
76. Williams TM, Stump CA, Nguyen DN, et al. Non-peptide calcitonin gene-related peptide receptor antagonists from a benzodiazepinone lead. Bioorg Med Chem Lett. 2006;16:2595–8.
77. Burgey CS, Paone DV, Shaw AW, et al. Synthesis of the (3R,6S)-3-amino-6-(2,3-difluorophenyl)azepan-2-one of telcagepant (MK-0974), a calcitonin gene-related peptide receptor antagonist for the treatment of migraine headache. Org Lett. 2008;10:3235–8.
78. Ho TW, Olesen J, Dodick DW, Kost J, Lines C, Ferrari MD. Antimigraine efficacy of telcagepant based on patient's historical triptan response. Headache. 2011;51:64–72.
79. Ho TW, Mannix LK, Fan X, et al. Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. Neurology. 2008;70:1304–12.
80. Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. Lancet. 2008;372:2115–23.
81. Ho TW, Ho AP, Chaitman BR, et al. Randomized, controlled study of telcagepant in patients with migraine and coronary artery disease. Headache. 2012;52:224–35.
82. Tepper SJ, Cleves C. Telcagepant, a calcitonin gene-related peptide antagonist for the treatment of migraine. Curr Opin Investig Drugs. 2009;10:711–20.
83. Ho TW, Connor KM, Zhang Y, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology. 2014;83:958–66.
84. Yao G, Yu T, Han X, Mao X, Li B. Therapeutic effects and safety of olcegepant and telcagepant for migraine: A meta-analysis. Neural Regen Res. 2013;8:938–47.
85. Silberstein SD. Emerging target-based paradigms to prevent and treat migraine. Clin Pharm Ther. 2012;93:78–85.
86. Diener HC, Barbanti P, Dahlof C, Reuter U, Habeck J, Podhorna J. BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. Cephalalgia. 2011;31:573–84.
87. Coloma MJ, Lee HJ, Kurihara A, et al. Transport across the primate blood-brain barrier of a genetically engineered chimeric monoclonal antibody to the human insulin receptor. Pharm Res. 2000;17:266–74.
88. Silberstein SD. Therapeutic monoclonal antibodies for migraine. US Neurol 2015;11 **(ePub)**.
89. Foltz IN, Karow M, Wasserman SM. Evolution and emergence of therapeutic monoclonal antibodies: what cardiologists need to know. Circulation. 2013;127:2222–30.
90. Wu H, Dall'Acqua WF. Humanized antibodies and their applications. Methods. 2005;36:1–2.
91. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol. 2014;13:885–92.
92. Goadsby PJ, Dodick DW, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, and Smith J Randomized, double-blind, placebo-controlled trial of ALD403, an anti-CGRP antibody in the prevention of frequent episodic migraine. In: 17th Congress of the International Headache Society, Valencia, 2015.
93. Dodick DW, Goadsby PJ, Silberstein SD, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol. 2014;13:1100–7.
94. Bigal ME, Edvinsson L, Rapoport A, Lipton R, Spierings E, Diener HC, Ma M, Hudson D, and Silberstein S A multicenter, randomized, double-blind, double-dummy, placebo-controlled, multi-dose study comparing the efficacy and safety of subcutaneous TEV-48125 with placebo for the preventive treatment of chronic migraine. In: 17th Congress of the International Headache Society, Valencia, 2015.
95. Lenz R, Silberstein S, Dodick D, Reuter U, Ashina M, Saper J, Cady R, Chon Y, Dietrich J, and Sun H Results of a randomized, double-blind, placebo-controlled, phase 2 study to evaluate the efficacy and safety of AMG 334 for the prevention of episodic migraine. In: 17th Congress of the International Headache Society, Valencia, 2015.
96. Bigal ME, Ferrari M, Silberstein SD, Lipton RB, Goadsby PJ. Migraine in the triptan era: lessons from epidemiology, pathophysiology, and clinical science. Headache. 2009;49(Suppl 1):S21–33.
97. Walter S, Alibhoy A, Escandon R, Bigal ME. Evaluation of cardiovascular parameters in cynomolgus monkeys following IV administration of LBR-101, a monoclonal antibody against calcitonin gene-related peptide. MAbs. 2014;6:871–8.
98. Bigal ME, Walter S, Bronson M, Alibhoy A, Escandon R. Cardiovascular and hemodynamic parameters in women following prolonged CGRP inhibition using LBR-101, a monoclonal antibody against CGRP. Cephalalgia. 2014;34(12):968–76.
99. Zeller J, Poulsen KT, Sutton JE, et al. CGRP function-blocking antibodies inhibit neurogenic vasodilatation without affecting heart rate or arterial blood pressure in the rat. Br J Pharmacol. 2008;155:1093–103.
100. Bigal ME, Escandon R, Bronson M, et al. Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: results of the Phase 1 program. Cephalalgia. 2013;34:483–92.

101. Feuerstein G, Willette R, Aiyar N. Clinical perspectives of calcitonin gene related peptide pharmacology. Can J Physiol Pharmacol. 1995;73:1070–4.
102. Sur C, Hargreaves R, Bell I, et al. CSF levels and binding pattern of novel CGRP receptor antagonists in rhesus monkey and human central nervous system: toward the development of a PET tracer. Cephalalgia. 2009;29:136–7.
103. Hostetler ED, Joshi AD, Sanabria-Bohorquez S, et al. In vivo quantification of calcitonin gene-related peptide receptor occupancy by telcagepant in rhesus monkey and human brain using the positron emission tomography tracer [11C]MK-4232. J Pharmacol Exp Ther. 2013;347:478–86.
104. Vermeersch SG, deHoon J, deSaint-Hubert B, et al. PET imaging in healthy subjects and migraineurs suggests CGRP receptor antagonists do not have to act centrally to achieve clinical efficacy. J Headache and Pain. 2013;14:224 **(Abstract)**.
105. Edvinsson L. CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. Br J Clin Pharmacol. doi:10.1111/bcp.12618 **[Epub ahead of print]**
106. Kaube H, Hoskin KL, Goadsby PJ. Inhibition by sumatriptan of central trigeminal neurones only after blood-brain barrier disruption. Br J Pharmacol. 1993;109:788–92.
107. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, et al. Cortical spreading depression activates and upregulates MMP-9. J Clin Invest. 2004;113:1447–55.
108. Zhang X, Levy D, Noseda R, Kainz V, Jakubowski M, Burstein R. Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. J Neurosci. 2010;30:8807–14.
109. Zhang X, Levy D, Kainz V, Noseda R, Jakubowski M, Burstein R. Activation of central trigeminovascular neurons by cortical spreading depression. Ann Neurol. 2011;69:855–65.
110. Tozzi A, de Iure A, Di Filippo M, et al. Critical role of calcitonin gene-related peptide receptors in cortical spreading depression. Proc Natl Acad Sci USA. 2012;109:18985–90.
111. Piper RD, Edvinsson L, Ekman R, Lambert GA. Cortical spreading depression does not result in the release of calcitonin gene-related peptide into the external jugular vein of the cat: relevance to human migraine. Cephalalgia. 1993;13:180–3.
112. De FM, Ossipov MH, Wang R, et al. Triptan-induced latent sensitization: a possible basis for medication overuse headache. Ann Neurol. 2010;67:325–37.
113. De FM, Porreca F. Opiate-induced persistent pronociceptive trigeminal neural adaptations: potential relevance to opiate-induced medication overuse headache. Cephalalgia. 2009;29:1277–84.
114. Michot B, Bourgoin S, Viguier F, Hamon M, Kayser V. Differential effects of calcitonin gene-related peptide receptor blockade by olcegepant on mechanical allodynia induced by ligation of the infraorbital nerve vs the sciatic nerve in the rat. Pain. 2012;153:1939–48.
115. Drummond PD. A quantitative assessment of photophobia in migraine and tension headache. Headache. 1986;26:465–9.
116. Noseda R, Burstein R. Advances in understanding the mechanisms of migraine-type photophobia. Curr Opin Neurol. 2011;24:197–202.
117. Noseda R, Kainz V, Jakubowski M, et al. A neural mechanism for exacerbation of headache by light. Nat Neurosci. 2010;13:239–45.
118. Maleki N, Becerra L, Upadhyay J, Burstein R, Borsook D. Direct optic nerve pulvinar connections defined by diffusion MR tractography in humans: implications for photophobia. Hum Brain Mapp. 2012;33:75–88.