The Journal of Headache and Pain

REVIEW

Open Access

Is there a role of calcitonin gene-related peptide in cortical spreading depression mechanisms?– Argument pro

Marina Romozzi[1,2*] and Paolo Calabresi[1,2*]

Migraine ranks as one of the most debilitating medical conditions worldwide, characterized by debilitating headaches associated with a plethora of accompanying symptoms [1, 2]. Approximately one-third of the patients with migraine experience aura, a reversible neurological phenomenon that manifests with visual, sensory, speech, and motor neurologic symptoms, usually lasting 5–60 min, either preceding or accompanying headache pain [3]. Cortical spreading depression (CSD), originally described by Leão in 1944 in a rabbit model, is a wave of depolarization of neuronal and glial cells spreading across the cerebral cortex at a rate of 2–5 mm/min, followed by a long period of hyperpolarization, has been proposed as the pathophysiological mechanism of migraine aura [4].

The depolarization typical of CSD is associated with local ionic shifts and neurotransmitter and metabolite release [5]. This includes the massive increases in extracellular potassium, intracellular sodium and calcium, and glutamate release [5]. Among the neurotransmitters, glutamate is prominent in initiating and propagating CSD by activating N-methyl-D-aspartic acid (NMDA) receptors [6, 7]. Vascular reactivity and blood flow modifications follow the change in neuronal excitability, with an increase in regional cerebral blood flow for 3–5 min, followed by hypoperfusion (spreading oligemia) lasting for approximately 1–2 h [8, 9].

Experimental evidence shows that CSD results in the activation of trigeminovascular neurons in a temporal way that resembles the onset of headache after aura in patients [10]. This suggests that activation of the trigeminovascular system (TGVS) is crucial for initiating migraine attacks [10]. The activation leads to the release of neuropeptides, such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP). The resultant arteriolar vasodilation, neurogenic inflammation, and mast cell degranulation may contribute to the activation or sensitization of dural nociceptors [11–13]. Evidence of CSD, as the underlying mechanism of aura, was shown in humans by functional magnetic resonance imaging (fMRI) [14, 15]. However, the existence of a relationship between CSD mechanisms and the subsequent head pain remains debated [13].

Calcitonin gene-related peptide, discovered in 1982, is a 37-amino acid vasodilator peptide that belongs to the calcitonin peptide family and is produced in peripheral sensory neurons and multiple sites throughout the CNS [16], that has been regarded as a target for the development of acute and prophylactic treatment for migraine [17]. It is the most abundant neuropeptide within the TGVS, where it is expressed in 50% of neurons in the human trigeminal ganglia [18].

The first evidence supporting the involvement of CGRP in the pathogenesis of migraine dates back to 1990, when elevated CGRP levels were observed during spontaneous migraine attacks in the external jugular blood, into which extracerebral tissues drain [19]. In 1993, it was discovered that stimulation of the trigeminal ganglion

*Correspondence:
Marina Romozzi
marinaromozzi@gmail.com
Paolo Calabresi
paolo.calabresi@policlinicogemelli.it
[1]Dipartimento Universitario di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy
[2]Neurologia, Dipartimento di Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

in cats resulted in the release of CGRP [20]. Both human and animal studies have shown that CGRP levels were significantly reduced by sumatriptan, in parallel with the relief of migraine symptoms in humans [20]. Additional evidence that CGRP has a role in migraine derives from clinical studies in which the infusion of exogenous CGRP could trigger migraine attacks in patients prone to migraine, suggesting a causative role of this peptide [21, 22].

More recently, several studies have confirmed elevated levels of CGRP in plasma, serum, saliva, tear fluid, and cerebrospinal fluid (CSF) in ictal and interictal phases in migraine patients compared to healthy controls [23, 24].

Lastly, the strongest *ex adiuvantibus* implication of CGRP in migraine comes from the development of treatments targeting the CGRP pathway, including monoclonal antibodies against the CGRP receptor or ligand (anti-CGRP mAbs) and small molecule antagonists of the CGRP receptor (i.e., gepants), that have shown safety and effectiveness as prophylactic and acute therapy for of migraine [25]. The role of CGRP in CSD mechanisms has been a matter of debate.

Relation between CSD and CGRP in animal models

The hypothesis that CGRP is only involved in the pain phase of migraine is reductive. There are several preclinical lines of evidence to support the involvement of CGRP in CSD processes and migraine aura, as well as the coupling of CSD with the activation of the TGVS in migraine pathophysiology with the subsequent release of CGRP from peripheral terminals [26, 27]. These hypotheses are supported by the loss of CSD-dependent neurogenic inflammatory response observed after sensory denervation of the meninges [28].

CGRP could also be released centrally in the cerebral cortex, influencing neural activity and vascular tone [29–31]. Tozzi and colleagues demonstrated that, in rat brain, endogenous CGRP was released in a calcium-dependent manner during potassium-induced CSD [6]. Three CGRP receptor antagonists (MK-8825, olcegepant, and CGRP 8–37) determined a dose-dependent inhibitory effect on CSD in neocortical slices, suggesting a pivotal role of CGRP in this event [6]. Interestingly, in this study, CSD was also blocked by NMDA but not AMPA receptor antagonists. Moreover, this phenomenon was also inhibited by topiramate but not carbamazepine [6]. Similarly, preliminary evidence showed that the systemic administration of olcegepant to mice in vivo inhibited repetitive CSD and altered the vascular response to CSD [32]. Fremanezumab, given intravenously in anesthetized rats, prevented the activation and sensitization of high-threshold trigeminovascular neurons by CSD [33]. The intraperitoneal application of MK-8825 in awake rats with intact blood-brain barrier (BBB), instead, failed to block CSD waves in the cortex and the CSD-associated hemodynamic changes but reversed the CSD-induced behaviors associated with pain and blocked the neuronal activation in the spinal trigeminal nucleus [34]. Lastly, exogenous CGRP in mice brain slices reversed the effects of prolonged CSD latency caused by anti-CGRP antibodies [35].

This data supports the hypothesis that CGRP antagonists could act directly or indirectly at a central level [6].

CSD also seems to influence CGRP expression and synthesis. Repeated experimental-induced CSD events increased CGRP mRNA and peptide levels at 24 h post-CSD in the rat cortex ipsilaterally [29]. In agreement, induced CSD in rats significantly enhanced CGRP expression in both protein and mRNA levels in the trigeminal ganglion [36, 37]. In a mouse model of migraine, CSD was also able to induce substantial changes in CSF composition, with 11% of the CSF proteome being altered in concentration, with up-regulation of proteins involved in the activation of receptors in the trigeminal ganglion [38]. Among these ligands, CGRP doubled in concentration [38]. The authors proposed that the CSF transport of CGRP to the trigeminal ganglion could be directly involved in the development of migraine headache [38].

An elevation of CGRP synthesis in association with CSD might contribute to an increased susceptibility to migraine through a positive feedback, where CSD triggers CGRP release and synthesis, thereby increasing the probability of subsequent CSD and migraine events.

CGRP may also mediate the coupling between neuronal activity and cerebral hyperemia observed during CSD [30, 31]. In a rabbit and cat model of CSD, the topical administration of an inhibitor of the CGRP receptor, [8–37], reduced CSD-induced pial dilation [30, 31]. In accordance with these findings, brain topical application of a CGRP receptor antagonist also decreased hyperperfusion associated with CSD [39]. These results suggest that CGRP may act as a vascular modulator of CSD, and the local release of CGRP in the meninges could contribute to CSD-induced dilation. In this view, there could be a bidirectional relationship where modifications in vascular tone can modulate neuronal activity, namely vascular-neuro coupling [40].

Human migraine models

Provocation experiments have demonstrated that intravenous infusion of CGRP can induce migraine-like attacks in patients with migraine, with and without aura [41]. Even to a lesser extent, CGRP provocation experiments have also been conducted in patients with aura [41]. In patients who experienced only migraine attacks with typical aura, CGRP infusion triggered migraine-like attacks without aura in 57% of patients, with four (28%) reporting typical aura symptoms [42].

In an open-label, single-arm, non-randomized trial, CGRP was administered intravenously to 34 patients with migraine with aura. Thirteen (38%) of 34 participants developed an attack of migraine with aura after CGRP infusion [43]. The authors hypothesized that CGRP acts on meningeal arteries, initiating the transmission of nociceptive information that reaches the somatosensory cortex and other cortical/subcortical areas implicated in the perception of migraine pain. In susceptible individuals, excitatory stimuli reaching regions like the visual cortex may reach the threshold for triggering CSD [43].

Altogether, these findings demonstrated that the majority of patients with migraine, with or without aura, developed delayed migraine-like attacks after the infusion of CGRP, including migraine aura episodes, indicative of a CGRP-related common cascade originating cephalic pain and aura in both phenotypes of patients.

Clinical evidence of the effectiveness of anti-CGRP mAbs in migraine aura

An indirect evidence of the role of CGRP in CSD is the effect of anti-CGRP mAbs in reducing the frequency and intensity of aura episodes. Anti-CGRP drugs show similar effectiveness in patients both with and without aura because they reduce the number of migraine attacks with aura in parallel with the reduction of migraine attacks without aura in both real-world studies and post-hoc analyses of clinical trials [44–48].

In post hoc analyses of clinical trials, the effectiveness of galcanezumab, eptinezumab, and erenumab was similar in patients with and without aura [46–48].

In other real-world prospective and retrospective studies or case series of patients with a diagnosis of migraine with aura treated with anti-CGRP mAbs, a reduced incidence, intensity, and duration of aura was observed regardless of the anti-CGRP mAb used or the type of migraine (episodic or chronic migraine) [44, 49, 50], with some studies showing a reduction in the number of auras regardless of responder status [51] or the complete disappearance of aura [52, 53].

A recent case series described the effectiveness of galcanezumab in patients with sporadic and familial hemiplegic migraine, with improvement in weakness symptoms in all patients except for two [54]. In line with these results, mice expressing a mutation in SCN1A, which is associated with familial hemiplegic type three in humans, exhibited spontaneous CSDs that propagate from the visual to the motor cortex [55]. CGRP and CGRP receptors are located throughout the CNS. Due to their dimension and peptidic nature, anti-CGRP mAbs and gepants poorly cross the BBB due to their molecular size [16, 56]. In rats, 0.1–0.3% of the plasma concentration of galcanezumab was found in the CNS [57].

Their action is thought to be through a peripheral site of action, and whether the action of CGRP blockade in migraine is mediated via central or peripheral mechanisms remains unclear [58]. The trigeminal ganglion has always been considered to lack BBB; therefore, it was thought it could represent the targets of gepants and anti-CGRP mAbs [16].

However, a recent paradigm shift study demonstrated that CSF carries solutes from the cortex to the trigeminal ganglion, facilitating nonsynaptic communication between the CNS and the periphery [38]. Furthermore, these observations are still preliminary, and it has not been elucidated whether the BBB remains intact during the course of spontaneous migraine attacks with aura or if it is uniformly tight throughout the brain, as specific regions may be less protected by the BBB than others [59].

Thus, if aura originates in the cortex, a direct action of anti-CGRP mAbs at this level remains to be demonstrated; alternatively, the inhibition of CGRP or CGRP receptor in the periphery could indirectly influence brain functioning, including CSD.

Response to Melo-Carrillo A. The Journal of Headache and Pain 2025 [60]

We appreciate the author's impressive and thorough review of the literature on this topic and the effort in supporting the "cons" hypothesis. We acknowledge the limitations in reproducing CSD in animal models that the author raised.

However, it remains challenging to dismiss the role of CGRP in CSD entirely, as evidence from electrophysiological, in vivo, and in vitro models suggests that CGRP may have a dual role, both centrally and peripherally [6]. This is further supported by the fact that CGRP antagonism may disrupt neurovascular coupling in CSD to the degree that it could reduce or even prevent the occurrence of neuronal and/or vascular events [30, 31].

In summary, in vitro studies demonstrate that endogenous CGRP was released during potassium-induced CSD and CGRP receptor antagonists inhibited CSD initiation [6], and in vivo studies revealed that topical administration of CGRP receptor antagonists reduced CSD-induced pial dilation and hyperperfusion associated with CSD [30, 31].

CGRP could also have an excitatory effect itself. Gimeno-Ferrer and colleagues demonstrated that topical application of CGRP in rats in vivo triggered episodes of local ictal discharge activity related to CSD that the CGRP receptor antagonist BIBN4096BS prevented. Similarly, in vitro recordings from slices of mouse cortex showed that the application of CGRP evoked periods of synchronized activity [61]. In the same study, topical

application of CGRP to rat cortex induced plasma extravasation [61].

Such excitatory effects of CGRP, producing repetitive action potentials, were also observed in other studies. Ryu and colleagues, in the immature rat in vitro spinal cord slice-dorsal root ganglion preparation, showed that application of CGRP produced a slow reversible depolarization in about one-third of the cells. The CGRP-evoked depolarization was associated with enhanced excitability in most neurons tested [62]. Similarly, in rat brain slices, Han and colleagues showed that CGRP increased excitatory postsynaptic currents in the amygdala and increased neuronal excitability. An NMDA receptor antagonist reversed CGRP-induced synaptic facilitation [63]. In vitro and in vivo models of non-migraine pain showed that CGRP receptor blockade in the amygdala directly inhibited NMDA-evoked, but not AMPA-evoked, membrane currents [64].

Altogether, these data suggest an important role of CGRP both in the regulation of neuronal excitability, possibly favoring CSD, and in the regulation of brain blood flow [61].

Furthermore, these findings reinforce the connection between central CGRP and the modulation of NMDA receptors and glutamate, as also demonstrated by Tozzi and colleagues, who showed that NMDA receptor antagonism inhibits CSD [6]. These mechanisms collectively enhance neural signaling in the cortex and mutually potentiate their effects [64]. Notably, glutamate, a key excitatory neurotransmitter, plays a fundamental role in CSD susceptibility, initiation, and propagation [65]. CGRP, functioning among other roles as a glutamatergic co-transmitter, contributes to sustaining dysfunctional neuronal excitation within the CNS, an event that is likely to occur in the brains of individuals with migraine [64].

A second key strength for CGRP implication in migraine CSD/aura is still the clinical evidence supporting the effectiveness of anti-CGRP mAbs in migraine aura. Indeed, anti-CGRP mAbs can be effective in reducing migraine with aura in parallel with the reduction of the number of migraine attacks [44–48]. However, increasing evidence reports a reduction in the number of auras regardless of the reduction of migraine days [51], or the complete disappearance of aura [52, 53], suggesting an independent and direct effect on the aura, which may not be mediated necessarily by a peripheral action.

Similarly, along with aura, findings on a positive effect of anti-CGRP mAbs on prodromal and accompanying symptoms have been reported in the literature, alongside aura frequency reduction [50, 66]. Some accompanying symptoms, such as photophobia or phonophobia, seem to be associated with higher levels of CGRP during migraine attacks [67].

In addition, intracerebroventricular administration of CGRP in transgenic mice (nestin/hRAMP1) caused a significant increase in light aversion prevented by CGRP receptor antagonist olcegepant [68].

These symptoms clearly originate within central structures, including the cortex, thalamus, brainstem, and hypothalamus [69]. However, as these regions lie beyond the BBB, the mechanism by which anti-CGRP mAbs, acting hypothetically at meningeal trigeminal afferents, prevent the development of migraine symptoms arising from the CNS, including aura, remains unclear. Furthermore, these symptoms frequently precede the activation of nociceptive trigeminovascular fibers and the subsequent migraine pain phase.

Comparably, other studies have shown neuroimaging and neurophysiological parameters changes with anti-CGRP mAbs [70, 71]. For example, Ziegeler and colleagues demonstrated through fMRI that erenumab led to a decrease in the activation of a specific network following trigeminal nociceptive input, including the secondary somatosensory cortex, the thalamus, and the insular cortex [70]. While a significant reduction of hypothalamic activation was found only in patients responders to erenumab [70].

These findings further support the notion that anti-CGRP mAbs mitigate "central symptoms" by inhibiting CGRP-mediated neurotransmission either directly or indirectly within the brain. Notably, radiolabeled galcanezumab has been shown to accumulate in the brain parenchyma and CSF of male rats, even if at low concentrations [57]. These findings cannot allow us to exclude that a small amount of active medication that reaches the CNS could be sufficient for a central effect. It is important to highlight that only 21 mg of erenumab significantly inhibits capsaicin-induced dermal blood flow (a model that assesses the target engagement of CGRP blocking agents), while the clinically approved dosages for migraine prophylaxis are 70 and 140 mg [72].

Furthermore, the status of the BBB during spontaneous migraine attacks with aura remains uncertain. Most neuroimaging studies have found no evidence of increased BBB permeability during aura, whereas animal models of CSD suggest a potential BBB alteration induced by CSD [73, 74]. However, it is important to highlight that certain structures within the circumventricular organs, which may lack BBB, such as the area postrema, have been shown in rat models to be functionally connected to key regions involved in migraine pathophysiology, including the hypothalamic nuclei and the spinal trigeminal nucleus. These regions may represent potential targets for anti-CGRP mAbs [75].

In conclusion, the available clinical and preclinical evidence does not allow us to rule out a significant role for CGRP in the mechanisms of CSD and its central

function. Targeting the CGRP pathway could also impact aura, the clinical manifestation of CSD.

Acknowledgements
MoH – RC_2025.

Author contributions
M.R. and P.C. wrote the manuscript.

Funding
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 6 February 2025 / Accepted: 23 March 2025
Published online: 28 April 2025

References

1. Burch RC, Buse DC, Lipton RB, Migraine (2019) Epidemiology, burden, and comorbidity. Neurol Clin 37(2019):631–649
2. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A et al (2022) Migraine. Nature Reviews Disease Primers.;8(2022):2
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia (2018);38(2018):1-211
4. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S (2017) Pathophysiology of migraine: A disorder of sensory processing. Physiol Rev 97(2017):553–622
5. Charles A, Brennan K (2009) Cortical spreading depression-new insights and persistent questions. Cephalalgia 29(2009):1115–1124
6. Tozzi A, de Iure A, Di Filippo M, Costa C, Caproni S, Pisani A et al (2012) Critical role of calcitonin gene-related peptide receptors in cortical spreading depression. Proc Natl Acad Sci U S A.;109(2012):18985-90
7. Close LN, Eftekhari S, Wang M, Charles AC, Russo AF (2018) Cortical spreading depression as a site of origin for migraine: role of CGRP. Cephalalgia 39(2018):428–434
8. Olesen J, Larsen B, Lauritzen M (1981) Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 9(1981):344–352
9. Lauritzen M, Skyhøj Olsen T, Lassen NA, Paulson OB (1983) Changes in regional cerebral blood flow during the course of classic migraine attacks. Ann Neurol 13(1983):633–641
10. Zhang X, Levy D, Noseda R, Kainz V, Jakubowski M, Burstein R (2010) Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. J Neurosci 30(2010):8807–8814
11. Brain SD, Williams TJ (1988) Substance P regulates the vasodilator activity of calcitonin gene-related peptide. Nature 335(1988):73–75
12. Dalkara T, Zervas NT, Moskowitz MA (2006) From spreading depression to the trigeminovascular system. Neurol Sci 27(Suppl 2):S86–90
13. Mehnert J, Fischer-Schulte L, May A (2023) Aura phenomena do not initiate migraine attacks-Findings from neuroimaging. Headache. (2023)
14. Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B et al (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A 98(2001):4687–4692
15. Sanchez del Rio M, Bakker D, Wu O, Agosti R, Mitsikostas DD, Ostergaard L et al (1999) Perfusion weighted imaging during migraine: spontaneous visual aura and headache. Cephalalgia.;19(1999):701-7
16. Edvinsson L, Haanes KA, Warfvinge K, Krause DN (2018) CGRP as the target of new migraine therapies — successful translation from bench to clinic. Nature Reviews Neurology.;14(2018):338– 50
17. Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A (2024) Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. Headache. (2024)
18. Eftekhari S, Salvatore CA, Calamari A, Kane SA, Tajti J, Edvinsson L (2010) Differential distribution of calcitonin gene-related peptide and its receptor components in the human trigeminal ganglion. Neuroscience 169(2010):683–696
19. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28(1990):183–187
20. Goadsby PJ, Edvinsson L (1993) The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 33(1993):48–56
21. Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J (2002) CGRP May play a causative role in migraine. Cephalalgia 22(2002):54–61
22. Christensen CE, Younis S, Deen M, Khan S, Ghanizada H, Ashina M (2018) Migraine induction with calcitonin gene-related peptide in patients from erenumab trials. The Journal of Headache and Pain.;19(2018):105
23. Kamm K, Straube A, Ruscheweyh R (2019) Calcitonin gene-related peptide levels in tear fluid are elevated in migraine patients compared to healthy controls. Cephalalgia 39(2019):1535–1543
24. Tesfay B, Karlsson WK, Moreno RD, Hay DL, Hougaard A (2022) Is calcitonin gene-related peptide a reliable biochemical marker of migraine? Curr Opin Neurol 35(2022):343–352
25. Al-Hassany L, Goadsby PJ, Danser AHJ, MaassenVanDenBrink A (2022) Calcitonin gene-related peptide-targeting drugs for migraine: how Pharmacology might inform treatment decisions. Lancet Neurol 21(2022):284–294
26. Close LN, Eftekhari S, Wang M, Charles AC, Russo AF (2019) Cortical spreading depression as a site of origin for migraine: role of CGRP. Cephalalgia 39(2019):428–434
27. Shatillo A, Koroleva K, Giniatullina R, Naumenko N, Slastnikova AA, Aliev RR et al (2013) Cortical spreading depression induces oxidative stress in the trigeminal nociceptive system. Neuroscience.;253(2013):341-9
28. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 8(2002):136–142
29. Wang Y, Tye AE, Zhao J, Ma D, Raddant AC, Bu F et al (2019) Induction of calcitonin gene-related peptide expression in rats by cortical spreading depression. Cephalalgia 39(2019):333–341
30. Colonna DM, Meng W, Deal DD, Busija DW (1994) Calcitonin gene-related peptide promotes cerebrovascular dilation during cortical spreading depression in rabbits. Am J Physiol Heart Circ Physiol 266(1994):H1095–H102
31. Wahl M, Schilling L, Parsons AA, Kaumann A (1994) Involvement of calcitonin gene-related peptide (CGRP) and nitric oxide (NO) in the Pial artery dilatation elicited by cortical spreading depression. Brain Res 637(1994):204–210
32. Eftekhari S, Kechechyan GM, Faas G, Charles A (2017) The CGRP receptor antagonist olcegepant modulates cortical spreading depression in vivo. Cephalalgia 37:295–296
33. Melo-Carrillo A, Noseda R, Nir RR, Schain AJ, Stratton J, Strassman AM, Burstein R (2017) Selective Inhibition of Trigeminovascular Neurons by Fremanezumab: A Humanized Monoclonal Anti-CGRP Antibody. J Neurosci.;37(2017):7149-63
34. Filiz A, Tepe N, Eftekhari S, Boran HE, Dilekoz E, Edvinsson L, Bolay H (2019) CGRP receptor antagonist MK-8825 attenuates cortical spreading depression induced pain behavior. Cephalalgia 39(2019):354–365
35. Jiang L, Wang Y, Xu Y, Ma D, Wang M (2018) The transient receptor potential Ankyrin type 1 plays a critical role in cortical spreading depression. Neuroscience 382(2018):23–34
36. Yisarakun W, Chantong C, Supornsilpchai W, Thongtan T, Srikiatkhachorn A, Reuangwechvorachai P, Maneesri-le Grand S (2015) Up-regulation of calcitonin gene-related peptide in trigeminal ganglion following chronic exposure to Paracetamol in a CSD migraine animal model. Neuropeptides 51(2015):9–16
37. Shibata M, Kitagawa S, Unekawa M, Takizawa T, Nakahara J (2023) Calcitonin Gene-Related Peptide mRNA Synthesis in Trigeminal Ganglion Neurons after Cortical Spreading Depolarization. Int J Mol Sci.;24(2023)

38. Kaag Rasmussen M, Møllgård K, Bork PAR, Weikop P, Esmail T, Drici L et al (2024) Trigeminal ganglion neurons are directly activated by influx of CSF solutes in a migraine model. Science 385(2024):80–86
39. Reuter U, Weber JR, Gold L, Arnold G, Wolf T, Dreier J et al (1998) Perivascular nerves contribute to cortical spreading depression-associated hyperemia in rats. Am J Physiol 274(1998):H1979–H1987
40. Kim KJ, Ramiro Diaz J, Iddings JA, Filosa JA (2016) Vasculo-Neuronal coupling: retrograde vascular communication to brain neurons. J Neurosci 36(2016):12624–12639
41. Ashina H, Schytz HW, Ashina M (2018) CGRP in human models of primary headaches. Cephalalgia 38(2018):353–360
42. Hansen JM, Hauge AW, Olesen J, Ashina M (2010) Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia 30(2010):1179–1186
43. Al-Khazali HM, Ashina H, Wiggers A, Rose K, Iljazi A, Christensen RH et al (2023) Calcitonin gene-related peptide causes migraine aura. J Headache Pain 24(2023):124
44. Mahović D, Bračić M, Jakuš L, Vukovic Cvetkovic V, Krpan M (2022) Effectiveness and safety of erenumab in chronic migraine: A Croatian real-world experience. Clin Neurol Neurosurg 214(2022):107169
45. Romozzi M, Burgalassi A, Vollono C, Albanese M, Vigani G, De Cesaris F et al (2024) Prospective evaluation of aura during anti-calcitonin gene-related peptide monoclonal antibody therapy after 52 weeks of treatment. Confinia Cephalalgica.;34(2024)
46. Igarashi H, Shibata M, Ozeki A, Matsumura T (2023) Galcanezumab effects on migraine severity and symptoms in Japanese patients with episodic migraine: secondary analysis of a phase 2 randomized trial. Neurol Ther 12(2023):73–87
47. Ashina M, McAllister P, Cady R, Hirman J, Ettrup A (2022) Efficacy and safety of eptinezumab in patients with migraine and self-reported aura: post hoc analysis of PROMISE-1 and PROMISE-2. Cephalalgia 42(2022):696–704
48. Ashina M, Goadsby PJ, Dodick DW, Tepper SJ, Xue F, Zhang F et al (2022) Assessment of erenumab safety and efficacy in patients with migraine with and without aura: A secondary analysis of randomized clinical trials. JAMA Neurol 79(2022):159–168
49. Straube A, Stude P, Gaul C, Schuh K, Koch M (2021) Real-world evidence data on the monoclonal antibody erenumab in migraine prevention: perspectives of treating physicians in Germany. J Headache Pain 22(2021):133
50. Iannone LF, De Cesaris F, Ferrari A, Benemei S, Fattori D, Chiarugi A (2022) Effectiveness of anti-CGRP monoclonal antibodies on central symptoms of migraine. Cephalalgia.;42(2022):1323-30
51. Ashina S, Melo-Carrillo A, Toluwanimi A, Bolo N, Szabo E, Borsook D, Burstein R (2023) Galcanezumab effects on incidence of headache after occurrence of triggers, premonitory symptoms, and aura in responders, non-responders, super-responders, and super non-responders. The Journal of Headache and Pain.;24(2023):26
52. Matteo E, Pensato U, Favoni V, Giannini G, Pierangeli G, Cevoli S (2021) Do anti-CGRP drugs have a role in migraine aura therapy? J Neurol.;268(2021):2273-4
53. Albanese M, Mercuri NB (2022) Could the New Anti-CGRP Monoclonal Antibodies Be Effective in Migraine Aura? Case Reports and Literature Review. J Clin Med.;11(2022)
54. Danno D, Ishizaki K, Kikui S, Takeshima T (2023) Treatment of hemiplegic migraine with anti-calcitonin gene-related peptide monoclonal antibodies: A case series in a tertiary-care headache center. Headache. (2023)
55. Jansen NA, Dehghani A, Linssen MML, Breukel C, Tolner EA, van den Maagdenberg A (2020) First FHM3 mouse model shows spontaneous cortical spreading depolarizations. Ann Clin Transl Neurol.;7(2020):132-8
56. Noseda R, Schain AJ, Melo-Carrillo A, Tien J, Stratton J, Mai F et al (2020) Fluorescently-labeled fremanezumab is distributed to sensory and autonomic ganglia and the dura but not to the brain of rats with uncompromised blood brain barrier. Cephalalgia 40(2020):229–240
57. Johnson KW, Morin SM, Wroblewski VJ, Johnson MP (2019) Peripheral and central nervous system distribution of the CGRP neutralizing antibody [(125)I] galcanezumab in male rats. Cephalalgia.;39(2019):1241-8
58. Basedau H, Sturm LM, Mehnert J, Peng KP, Schellong M, May A (2022) Migraine monoclonal antibodies against CGRP change brain activity depending on ligand or receptor target - an fMRI study. Elife.;11(2022)
59. Wiggers A, Ashina H, Hadjikhani N, Sagare A, Zlokovic BV, Lauritzen M, Ashina M (2022) Brain barriers and their potential role in migraine pathophysiology. J Headache Pain.;23(2022):16
60. Melo-Carrillo, A. (2025) Is there a role of calcitonin gene-related peptide in cortical spreading depression mechanisms?– Argument con. J Headache Pain 26 https://doi.org/10.1186/s10194-025-02012-4
61. Gimeno-Ferrer F, Eitner A, Bauer R, Lehmenkühler A, Edenhofer M-L, Kress M et al (2022) From spreading depolarization to epilepsy with neuroinflammation: The role of CGRP in cortex. Experimental Neurology.;356(2022):114152
62. Ryu PD, Gerber G, Murase K, Randic M (1988) Actions of calcitonin gene-related peptide on rat spinal dorsal Horn neurons. Brain Res 441(1988):357–361
63. Han JS, Adwanikar H, Li Z, Ji G, Neugebauer V (2010) Facilitation of Synaptic Transmission and Pain Responses by CGRP in the Amygdala of Normal Rats. Molecular Pain.;6(2010):1744-8069-6-10
64. Han JS, Li W, Neugebauer V (2005) Critical role of calcitonin gene-related peptide 1 receptors in the amygdala in synaptic plasticity and pain behavior. J Neurosci.;25(2005):10717-28
65. Hoffmann J, Charles A (2018) Glutamate and its receptors as therapeutic targets for migraine. Neurotherapeutics 15(2018):361–370
66. Alpuente A, Torre-Sune A, Caronna E, Gine-Cipres E, Torres-Ferrús M, Pozo-Rosich P (2023) Impact of anti-CGRP monoclonal antibodies on migraine attack accompanying symptoms: A real-world evidence study. Cephalalgia.;43(2023):3331024231177636
67. Alpuente A, Gallardo VJ, Asskour L, Caronna E, Torres-Ferrus M, Pozo-Rosich P (2022) Salivary CGRP can monitor the different migraine phases: CGRP (in) dependent attacks. Cephalalgia 42(2022):186–196
68. Recober A, Kuburas A, Zhang Z, Wemmie JA, Anderson MG, Russo AF (2009) Role of calcitonin gene-related peptide in light-aversive behavior: implications for migraine. J Neurosci 29(2009):8798–8804
69. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ (2014) Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain 137(2014):232–241
70. Ziegeler C, Mehnert J, Asmussen K, May A (2020) Central effects of erenumab in migraine patients: An event-related functional imaging study. Neurology.;95(2020):e2794-e802
71. de Tommaso M, La Rocca M, Quitadamo SG, Ricci K, Tancredi G, Clemente L et al (2022) Central effects of galcanezumab in migraine: a pilot study on Steady State Visual Evoked Potentials and occipital hemodynamic response in migraine patients. The Journal of Headache and Pain.;23(2022):52
72. Vu T, Ma P, Chen JS, de Hoon J, Van Hecken A, Yan L et al (2017) Pharmacokinetic-Pharmacodynamic Relationship of Erenumab (AMG 334) and Capsaicin-Induced Dermal Blood Flow in Healthy and Migraine Subjects. Pharm Res.;34(2017):1784-95
73. Schankin CJ, Maniyar FH, Seo Y, Kori S, Eller M, Chou DE et al (2016) Ictal lack of binding to brain parenchyma suggests integrity of the blood-brain barrier for 11 C-dihydroergotamine during Glyceryl trinitrate-induced migraine. Brain 139(2016):1994–2001
74. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, Bolay H, Bermpohl D, Jin H et al (2004) Cortical spreading depression activates and upregulates MMP-9. J Clin Invest.;113(2004):1447-55
75. Shapiro RE, Miselis RR (1985) The central neural connections of the area Postrema of the rat. J Comp Neurol 234(1985):344–364

Publisher's note