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REVIEW

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Unmasking the relationship between CGRP and glutamate: from peripheral excitation to central sensitization in migraine

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Abstract

The exact mechanisms that trigger the activation of the trigeminovascular system in migraine remain unclear. The involvement of calcitonin gene-related peptide (CGRP) in migraine is well-documented, and treatments aimed at blocking CGRP activity have proven successful in reducing migraine attacks for some patients. However, around one third of individuals do not respond to these therapies, which are also limited by factors like cost, side effects, and contraindications. There is growing evidence suggesting that glutamate, an excitatory neurotransmitter, plays a crucial role in the onset and maintenance of migraine pain, partially by enhancing CGRP release. Increased glutamate levels have been linked to both peripheral and central sensitization, potentially contributing to the development and persistence of chronic migraine. The relationship between CGRP and glutamate is complex, with glutamate possibly acting as an upstream trigger for CGRP release. This review examines the interplay between CGRP and glutamate, and their involvement in both peripheral and central sensitization. It also explores the therapeutic potential of targeting either glutamate or CGRP, aiming to address both peripheral and central migraine mechanisms. Finally, the role of triggers in migraine initiation at the peripheral level is discussed, offering insights into potential preventive strategies.

Keywords Migraine, CGRP, Excitotoxicity, Glutamate, NMDA

Introduction

Activation of the trigeminovascular system is a key pathological event in the initiation of a migraine attack [1]. Current evidence suggests that migraine pain originates peripherally, with the activation of nociceptive neurons innervating the dura mater [2]. However, the exact mechanisms that trigger this activation remain uncertain. Preclinical and clinical studies have identified calcitonin gene-related peptide (CGRP) as a crucial player in nociception [3, 4]. Its critical role in migraine pathophysiology is further supported by the promising results of pharmacological interventions targeting CGRP activity, which prevent migraine attacks by either blocking receptor-binding sites or modulating neuropeptide levels [5–7]. However, about 25–30% of patients still do not respond to these medications, leading to treatment discontinuation [8–11]. Additionally, their use is further limited by factors such as cost, side effects, and contraindications [12–16]. Notably, these treatments exert their effects mainly peripherally, without crossing the blood-brain barrier (BBB), which supports the idea of the peripheral origin of migraine attacks [17, 18]. While the

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peripheral origin of migraine is well-supported, central mechanisms should not be overlooked. Migraine attacks often begin with prodromal symptoms hours to days before headache onset, highlighting central involvement in early phases [19]. Additionally, some CGRP-targeted antibodies can cross BBB to some extent and exert central effects [20, 21].

The precise mechanisms through which CGRP contributes to the pain process remain to be fully clarified. An intriguing animal study demonstrated that while topical and systemic administration of CGRP significantly increased dural blood flow, neither method resulted in the activation or sensitization of meningeal nociceptors [22]. This suggests that CGRP's vasodilatory effect in the meninges may be insufficient alone to trigger or sensitize nociceptors, indicating that we may be overlooking another critical element in the pain cascade. Glutamate, the brain's primary excitatory neurotransmitter, could be this missing link [23, 24]. Animal models show that elevated glutamate levels reduce the mechanical force needed to activate trigeminovascular neurons and to increase dural blood flow [25, 26]. Known for its role in excitation, glutamate is abundant in pain pathways [23, 24] and plays a key role in initiating cortical spreading depression [26]. With the documented elevation in glutamate at both peripheral and central levels among migraine patients [27–29], it could be likely that glutamate could serve as a central driver in this cascade.

Glutamate and CGRP may both contribute to peripheral and central sensitization, driving not only the onset and persistence of migraine headaches, but also their progression to chronic migraine [30–32]. While their relationship is complex, in vitro and in vivo evidence supports the upstream effect of glutamate on CGRP release [33–36]. This raises the possibility that the current approach of targeting CGRP may interrupt the chain of events midstream, leaving the glutamate-driven upstream mechanisms unaddressed.

These insights bring up two important questions. First, by targeting CGRP peripherally, could central mechanisms persist via glutamate, potentially explaining why some patients do not respond to treatment, or why migraines are not fully eliminated even in responders? Second, could we achieve therapeutic benefits if we target glutamate's initial impact at the peripheral level? In this review, we aim to answer these questions by exploring the relationship between CGRP and glutamate, investigating which may act as the primary driver, and examining their roles in both the peripheral and central mechanisms of migraine. Additionally, we will discuss the clinical implications and challenges of targeting these neuro-messengers and provide insights into possible treatment strategies.

The trigeminovascular system

Peripheral endings of trigeminal fibers surround the dural blood vessels, forming a network which is highly responsive to vascular and neuronal changes, often referred to as the 'trigeminovascular system' [37]. In animal studies, stimulation of this system has been widely utilized to investigate the headache phase of migraine [37–39]. While it has already been established that activation of this pathway leads to pain perception, the initial triggers for this activation remain unclear.

The meninges, muscles, and blood vessels in the head receive extensive innervation from primary afferent neurons, which include myelinated Aδ fibers and unmyelinated C fibers [40]. The cell bodies of these afferent neurons are located in the sensory ganglia, including the trigeminal ganglion (TG) and cervical dorsal root ganglion [41–43]. Dorsal root ganglion and TG neurons are pseudo-unipolar, with axons that split to send signals both to the central area, including the dorsal horn or trigeminal nucleus caudalis (TNC), as well as to peripheral tissues near the dura [43, 44]. The TNC is a part of the brainstem and serves as the principal region for processing facial nociceptive signals from the trigeminal nerve [45]. The trigeminal nerve comprises three branches to the forehead and face: the ophthalmic, maxillary, and mandibular nerves [46]. Initial anatomical studies showed that many of the dural vascular structures are innervated by the Aδ- and C-fibers arising from the ophthalmic branch of the trigeminal nerve [47, 48]. In contrast, the cervical dorsal root ganglia of the C1-C3 nerves primarily innervate the back of the head and upper neck [49].

Primary afferents from the dura and posterior regions of the head and neck, project to the trigeminal cervical complex, a region that encompasses the spinal trigeminal nucleus in the brainstem and spinal cord segments C1 to C3 [43, 50, 51]. Therefore, the trigeminal cervical complex functions as the primary relay center for nociceptive information within the head [52]. Research on animal models has demonstrated that stimulating dural blood vessels enhances neuronal excitability, as well as increases metabolic activity and blood flow within the trigeminal cervical complex [53–55]. The nociceptive pathway continues as second-order neurons in the trigeminal cervical complex project along the ascending trigeminothalamic tract to third-order neurons in the thalamus, particularly the ventroposteromedial and posterior thalamic nuclei [56]. These thalamic neurons relay pain-related sensory and discriminatory information to the primary somatosensory cortex, where the perception of pain is processed and integrated [57].

Key evidence for the trigeminal system's role in migraine headaches is that effective treatments, like the hydrophilic drug sumatriptan, and preventive therapies,

such as botulinum toxin and CGRP monoclonal antibodies, do not cross the BBB [58–60]. Thus, these treatments work by inhibiting nociceptive signaling from peripheral trigeminal fibers in the dura [61]. Similar to blood vessels in the dura, the TG is located outside of the BBB; therefore, all protection provided by the BBB is not present for the cell bodies of these trigeminal afferents [62] (Fig. 1). In addition to dura and TG, certain parts of the brainstem, such as the area postrema, are not protected by the BBB. In a non-human primate study by Eftekhari et al., CGRP receptor expression and binding of a CGRP receptor antagonist were observed in some of these brainstem regions [63].

Glutamate: an initiator of the trigeminovascular system

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS), essential for most brain functions [64, 65], and implicated in various neurological disorders including migraine [66–71]. It is stored in synaptic vesicles via a proton gradient-dependent system, with three vesicular glutamate transporters identified so far [72]. Upon neuronal stimulation, glutamate is released into the synapse through exocytosis, briefly raising its concentration and activating glutamate receptors [72]. Although glutamate is crucial for normal signal transduction in the nervous system, excessive accumulation of glutamate in the synaptic space can lead to excitotoxicity. Excitotoxicity refers to excessive activation of glutamate receptors and sustained neuronal excitation, leading to neuronal damage and ultimately cell death [73]. Glutamate receptors are classified into two types: ionotropic and metabotropic [74]. Ionotropic glutamate receptors (iGluRs) are fast-acting, ligand-gated channels, further classified into N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and kainic acid receptors. These have rapid excitatory effects. Metabotropic glutamate receptors (mGluRs), on the other hand, are G-protein-coupled and include eight subtypes (mGluR1-8) grouped into three categories (I-III) based on their effects on second messengers and pharmacology. Group I is linked to slow excitation, while groups II and III are involved in slow inhibition [74].

It is widely recognized that glutamate facilitates fast synaptic transmission from primary afferents to second-order nociceptive neurons [75]. Animal and human localization studies have demonstrated that NMDA, AMPA, kainate, and mGlu receptors are present within the trigeminal system [24, 76, 77]. Also, at the level of the spinal cord, all ionotropic glutamate receptors are found in both the dorsal horn [78] and the dorsal root ganglion [79, 80]. Glutamate receptors are present not only in the trigeminal cervical complex and TG, but also in other pain-modulating brain regions such as the thalamus, hypothalamus, and periaqueductal gray [81, 82]. Specifically, high concentrations of NMDA-positive neurons are found in major structures involved in migraine pain, such as the TG, TNC, and thalamus; suggesting a possible link between NMDA receptor activity and the underlying mechanisms of migraine [81, 82]. In the trigeminal nociceptive system, glutamate stored in small synaptic vesicles can be released by presynaptic spikes, activating AMPA and NMDA receptors on the postsynaptic nociceptive neurons in the TNC [24] or in dorsal horn neurons of the upper cervical segments [83, 84].

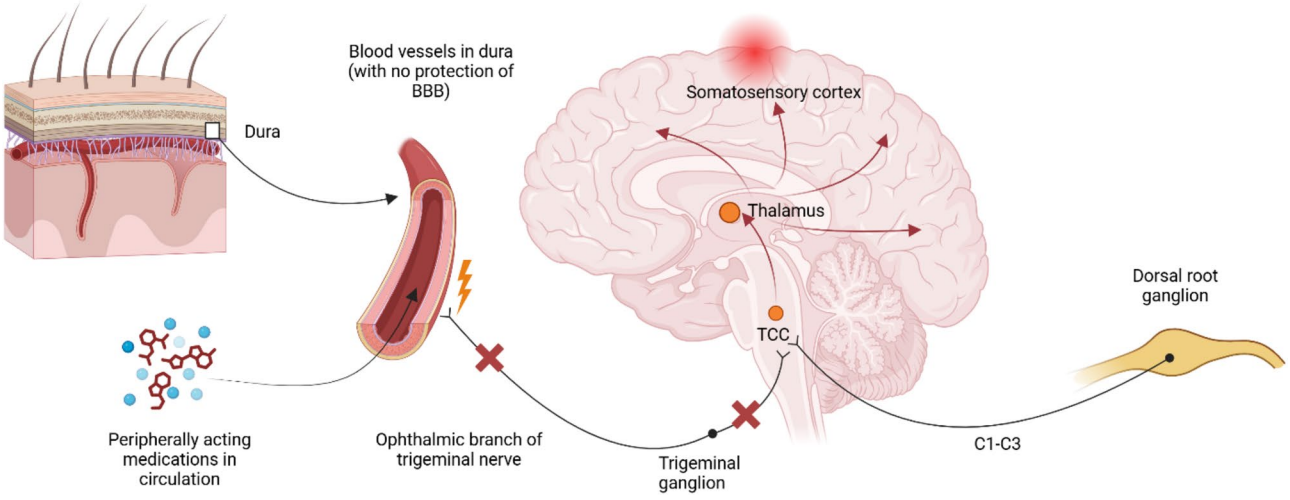

Fig. 1 Peripheral model of migraine initiation. Activated primary afferents innervating blood vessels of the dura transmit signals to the TCC, a relay center in the brainstem. The TCC also receives input from the cervical dorsal root ganglia of the C1-C3 nerves, which primarily innervate the back of the head and upper neck. Second-order neurons then relay signals from the brainstem to the thalamus, which projects them to various regions of the somatosensory cortex, where pain perception occurs. Effective medications with inability to cross BBB are believed to prevent the attack by inhibition of sensory nerves at the level of the meninges. *BBB, blood-brain barrier; TCC, trigeminal cervical complex. C1-C3: cervical nerves.* Created in https://BioRender.com

Applying a selective small fiber excitant (mustard oil), into the temporomandibular joint region in rats activates small trigeminal C-fibers and triggers the acute release of glutamate and aspartate in the TNC at the synapse with second-order neurons [85]. In support of glutamate's role in migraine, the genes identified with familial hemiplegic migraine all encode proteins that regulate glutamate availability at synaptic terminals, ultimately enhancing neuronal excitability [86].

Peripheral trigeminal nociceptive signaling from the meninges is now regarded as a primary mechanism underlying migraine pain [2]. Interestingly, in addition to glutamate's well-known role in transmitting nociceptive signals from primary afferents to the central area of the brain, previous findings support the role of glutamate as a peripheral pro-nociceptive agent in the trigeminal system [87–89]. The presence of NMDA receptors has been observed in nerve fibers that innervate dural blood vessels [90]. In line with the anatomical findings, the role of NMDA receptors in the activation of trigeminal afferents that innervate the meninges, has also been reported [90, 91]. In an interesting study by Guerrero et al., they revealed that glutamate and aspartate (both activators of NMDA receptors) successfully activated isolated TG neurons, suggesting functional NMDA receptor expression in first-order nociceptors [91]. Additional evidence supporting the role of peripheral glutamatergic system dysregulation in migraine development comes from studies showing elevated plasma glutamate levels in individuals with migraine [27, 28, 92]. This increase is present both during migraine attacks and in interictal periods [28, 93], impacting individuals with and without aura [93, 94].

Glutamate and vasodilation

Interestingly, glutamate can cause vasodilation, a phenomenon commonly related to migraine, which for many years was believed to be the main cause of migraine. The connection between glutamate and nitric oxide (NO) was first suggested when it was observed that treatment with glutamate or NMDA led to the release of NO and cyclic guanosine monophosphate (cGMP) in cerebellar cultures [95]. Furthermore, activation of NMDA receptors increases cGMP levels in the brain, a process that can be blocked by nitric oxide synthase inhibitors and NO scavengers, indicating that NO plays a downstream signaling role after NMDA receptor activation [95]. In neurons, Ca^{2+} influx resulting from NMDA receptor activation stimulates nitric oxide synthase, which is physically coupled to NMDA receptors [96]. Additionally, glutamate can activate NMDA receptors on endothelial cells in capillaries, triggering nitric oxide synthase induction and NO release, which promotes vasodilation [97].

CGRP: a vasodilator and amplifier in the trigeminovascular system

Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide that functions as a neuromodulator. Both preclinical and clinical research indicates that CGRP is closely linked to brain nociception, though the precise mechanisms remain uncertain [98, 99]. However, it is well-established that CGRP can act as a powerful vasodilator [100]. CGRP receptors are G-protein coupled receptors and when CGRP binds to these receptors on artery smooth muscle cells, it triggers an increase in intracellular cyclic adenosine monophosphate (cAMP), leading to muscle relaxation and vasodilation [101].

The CGRP receptor is found on dural vascular smooth muscle cells, neurons, and satellite glial cells in the TG, TNC, and dorsal horns of the spinal cord [102, 103]. More specifically, they are present on Aδ fibers which are large-diameter myelinated TG neurons that do not produce CGRP, as well as on surrounding satellite glial cells [104]. In this regard, meningeal Aδ fibers possess CGRP receptors, whereas meningeal C fibers do not [105]. Unlike the CGRP receptor, CGRP itself is almost exclusively expressed in neurons, especially in sensory nerves [104]. CGRP is predominantly synthesized in unmyelinated C fibers within the trigeminovascular system [105]. These CGRP-expressing fibers are afferent (meaning that signaling is coming from the periphery and moving toward the brain), originating from the dorsal root ganglion and the TG, reaching both intracranial and extracranial regions of the head, including the dura [106]. These sensory fibers are polymodal in nature as they can be activated with thermal, chemical, and high-threshold mechanical stimuli [107]. Therefore, in response to the mentioned stimuli, a local axon reflex occurs, allowing these sensory fibers to release CGRP [108]. As mentioned earlier, dorsal root ganglion and TG neurons are pseudounipolar, with axons that split to send signals both to the central area, including the dorsal horn or TNC, and to peripheral tissues [44]. This distinctive structure enables the release of neurotransmitters/neuromodulators at both central and peripheral sites, facilitating two-way communication between the terminals [44].

The direct role of CGRP in activating meningeal afferents has been disproven to some extent. When CGRP is applied locally to the rodent dura mater, it does not induce firing or immediate sensitization of meningeal afferents, though cAMP analogs can effectively sensitize them [22, 109]. This lack of activation likely results from the absence of functional CGRP receptors on nerve fibers innervating the dura mater. As Lennerz et al. showed in the cranial dura mater, immunoreactivity for CGRP receptor components was observed in arterial blood vessels, mononuclear cells, and Schwann cells, but was absent in sensory axons [110]. It is noteworthy that an

intriguing animal study demonstrated that CGRP preferentially activates and sensitizes trigeminal nociceptors in the dura of female mice, but not male mice [111]. Similarly, in another rodent model, intraspinal CGRP administration caused prolonged, dose-dependent mechanical hypersensitivity in female mice, whereas its effects in males were more transient [112]. Also, in hyperalgesic priming induced by interleukin-6, the CGRP receptor antagonist olcegepant, when administered intraspinally, blocked and reversed hyperalgesic priming exclusively in females [112]. These sex-specific effects of CGRP at both peripheral and central levels warrant further investigation.

Even direct injections of CGRP or its receptor antagonists into the rat TG, fail to alter the activity or mechanical sensitivity in neurons within the spinal trigeminal nucleus that receives meningeal input [113]. However, systemic administration and iontophoretic application of CGRP receptor antagonists in the spinal trigeminal nucleus effectively reduces spinal trigeminal activity [98], suggesting that CGRP primarily activates trigeminovascular neurons at their synapses within the trigeminal nucleus [114]. Direct injection of CGRP receptor antagonists into the periaqueductal gray inhibited nociceptive trigeminovascular activation, suggesting that central descending mechanisms from this region play a role in the action of CGRP and its receptor antagonists in controlling head pain [115]. This lack of a direct hyperalgesic effect may be considered paradoxical given the effectiveness of peripheral antibodies targeting CGRP and/or its receptor. It is possible that CGRP indirectly modulates central trigeminal nociceptive transmission, likely through other mediators. It should be noted that genetic mapping studies have not linked migraine to variations in the CGRP gene [116], and a genome-wide association study has similarly failed to implicate the CGRP or CGRP receptor genes [117]. Additionally, the infusion of other chemicals, such as glyceryl trinitrate, histamine, and pituitary adenylate cyclase-activating peptide, can induce delayed migraine-like headaches in migraineurs, similar to CGRP [118–121]. Overall, it is reasonable to conclude that CGRP plays a significant role in migraine pathophysiology, but it is certainly not the sole contributor.

CGRP and vasodilation

Release of CGRP from bidirectional trigeminal afferent C-fibers can activate CGRP receptors on nearby afferent Aδ fibers, which extend back to the TNC [44]. In the peripheral nervous system, CGRP's strong vasodilatory effect can expand meningeal arteries [100]. However, the idea that dural vasodilation directly causes pain is questioned for a few reasons. First, not all substances that dilate blood vessels induce migraine pain in humans; for instance, vasoactive intestinal peptide can cause cranial vasodilation without triggering migraine in migraineurs [122]. However, it should be mentioned that there are reports of headache induction by vasoactive intestinal peptide in healthy individuals and migraine patients without aura [123, 124]. Second, some migraine-inducing substances, despite their well-known vasodilatory properties, can trigger migraines independently of significant vasodilation. For example, a 3T magnetic resonance angiography study on migraine patients investigated vascular changes during nitroglycerin-induced migraine. The results showed no significant differences in the diameters of intracerebral arteries or extracerebral arteries compared to baseline. Additionally, blood vessel diameters remained consistent between headache and non-headache sides. Blood flow in the basilar and internal carotid arteries also remained unchanged during nitroglycerin infusion or later during migraine [125]. In a cross-sectional study of migraine patients examining within subject differences in the circumference of extracranial and intracranial arterial segments between attack and attack-free days, as well as between the pain and non-pain sides, migraine pain was not associated with extracranial arterial dilation and showed only slight intracranial dilation [126]. While both topical and systemic CGRP administration led to dilation of meningeal blood vessels, it did not trigger or sensitize meningeal pain receptors in the animal model [22]. In a double-blind, crossover study, 12 patients with migraine without aura received an intravenous infusion of either human α-CGRP or a placebo. The author concluded that while CGRP induced cerebral artery dilation, the extent of this effect was minimal, making it unlikely to be the sole mechanism underlying CGRP-induced migraine [127]. There are multiple potential scenarios which may be at play here. (1) Vasodilation alone may not activate the migraine pain pathway and may simply occur alongside meningeal nociceptor activation and the release of vasoactive peptides into meningeal blood vessels. (2) A greater amount of vasodilation may be necessary to induce pain, requiring a specific threshold to be reached. (3) Neuropeptide-induced vasodilation may trigger pain transmission when peripheral sensitization has already occurred in the primary afferent. (4) Different mechanosensitivity of nociceptors may alter response to vasodilation affecting the pain pathway, for example, Aδ fibers have greater mechanosensitivity than that of C-fibers [128]. In this case, vasodilation, which causes mechanical stretching of the blood vessel walls, is likely to have a stronger effect on activating Aδ fibers compared to C-fibers. In this latter case, blocking CGRP vasodilatory action could have a more pronounced effect on Aδ fibers, as CGRP receptors are present on vascular smooth muscle cells [105].

Although evidence has questioned whether dural vasodilation directly triggers pain, it may still influence

trigeminal primary afferent nociceptors. One proposed mechanism for how vascular signaling contributes to pain perception involves activation and sensitization through increased extracellular cations, primarily potassium [129]. It has been suggested that activation of either cAMP-mediated pathways (e.g., through CGRP) or cGMP-mediated pathways (e.g., through sildenafil) opens ATP-sensitive potassium channels on vascular smooth muscle cells in the walls of intracranial arteries, leading to vasodilation. This process results in the accumulation of positively charged ions in the extracellular space, creating an electrical gradient that drives these ions into neighboring trigeminal pain fibers, activating them [41]. Taken together, vasodilation is an important phenomenon observed during migraine, and its role in migraine pathophysiology should not be overlooked. However, some evidence continues to question whether it is the primary driver of pain. Instead, migraine pain may arise from a combination of vascular and neuronal factors, warranting further investigation into how these processes interact.

Studies exploring the relationship between glutamate and CGRP

The association between CGRP and glutamate has been mostly investigated in animal models so far (Table 1). The relationship between these two compounds demonstrates both upstream and downstream effects of glutamate that may be causing or mediating the effects of CGRP on migraine.

Glutamate's upstream role in CGRP release

An in vivo model in rats showed that increased glutamate levels in peripheral tissues like the temporalis muscle led to CGRP release [35]. This is in line with findings by Benbow et al. showing that administration of 1000 mg/kg monosodium glutamate (MSG) to rats, produced a prolonged increase in plasma glutamate and CGRP concentrations, followed by headache and nausea-like behaviors [33]. These findings make sense when considering the defensive role of the BBB, where individuals with an intact BBB have lower transport of glutamate from the blood into the brain [130]. As shown by Price et al., significantly elevated serum levels of glutamate or aspartate led to a notable net increase in the concentration of these amino acids in circumventricular organ regions of the brain, like the hypothalamus, which are thought to have little to no BBB protection; while no significant increase was observed in non-circumventricular organ regions [131]. Thus, in the case of a person having normal BBB function, glutamate can only exert its initiating nociception at the dura and TG levels. However, situations which cause BBB permeability, such as head injury [132], infection [133], stress [134], high substance P (SP) levels [135], neurotoxic exposure [136], and presence of

Table 1 Association between CGRP and glutamate in preclinical models relevant for migraine

Author, year	Population/ Model	Region	Key findings
Studies evaluating the impact of glutamate or its antagonists on CGRP release			
Gazerani, 2010, [35]	Rat/ in vivo	Temporalis muscle nociceptors	CGRP release was induced by elevated interstitial glutamate concentrations in the temporalis muscle.
Kageneck, 2014, [34]	Mouse/in vitro	Brainstem and dura mater	Glutamate receptor antagonist inhibited CGRP release from the brainstem while showing only a slight inhibitory effect in the TG and no effect in the dura mater.
Tringali, 2018, [36]	Rat/in vitro	Brainstem	Perampanel via AMPA antagonism inhibited basal CGRP release from isolated rat brainstem in a concentration-dependent manner.
Guerrero-Toro, 2021, [91]	Rat/in vivo	TG neurons	Neither glutamate nor NMDA changed the level of extracellular CGRP in TG.
Benbow, 2022, [33]	Rat/in vivo	Plasma	Systemic administration of MSG produced a prolonged increase in plasma glutamate and CGRP concentrations.
Studies evaluating the impact of CGRP or its antagonists on glutamate release or neuronal excitability			
Kangrga, 1990, [145]	Rat/in vitro	Spinal cord slice-dorsal root ganglion	CGRP induced a significant increase in the basal release of glutamate and aspartate, which was largely independent of calcium.
Ebersberger, 2000, [143]	Rat/in vivo	Dorsal horn neurons	When calcitonin gene-related peptide was administered, the responses of the neurons to the application of both NMDA and AMPA were increased.
Storer, 2004, [98]	Cat/in vivo	TNC neurons	CGRP antagonists inhibited the majority of units (26 of 38 cells) activated by L-glutamate, demonstrating a non-presynaptic site of action for CGRP.
Takhshid, 2007, [139]	Rat/in vitro	Dorsal spinal cord	CGRP caused increases in the K^+-evoked release of aspartate and glutamate.

CGRP: calcitonin gene-related peptide, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, TG: trigeminal ganglion, MSG: monosodium glutamate, NMDA: N-methyl-D-aspartic acid. TNC: trigeminal nucleus caudalis

excitotoxicity itself [137], could then allow glutamate to act both peripherally and centrally.

In the brainstem, glutamate receptor antagonists inhibit CGRP release, particularly through AMPA receptors, suggesting that glutamate receptor activation is required to stimulate CGRP release centrally [36]. In the study by Kageneck [34], they hypothesized that capsaicin-induced glutamate release may facilitate CGRP release that depends on Ca^{2+} through presynaptic glutamate auto-receptors. Ca^{2+}-permeable NMDA receptors could further increase Ca^{2+} levels in central afferent terminals, adding to the Ca^{2+} already introduced upon capsaicin stimulation via other channels. Interestingly, glutamate receptor antagonists significantly inhibited CGRP release in the brainstem, but only slightly in the TG, and not at all in the dura mater. This may imply a central mechanism where brainstem activation (via glutamate signaling) enhances CGRP release, influencing central pain processing in migraine.

CGRP's downstream effect on glutamate release and neuronal excitability

In the study by Kangrga et al., CGRP perfusion increased the basal release of glutamate and aspartate from rat spinal cord slices [138]. However, this CGRP-induced release was not affected by capsaicin treatment. Since capsaicin administration selectively destroys small neurons in the dorsal root ganglia, many of which contain neuropeptides such as SP and CGRP, this finding suggests that CGRP does not stimulate glutamate and aspartate release from capsaicin-sensitive primary afferents. Instead, the source of these excitatory neurotransmitters may be local interneurons or neighboring microglial cells. Similarly, in the study by Takhshid et al., CGRP was found to enhance K+-stimulated release of aspartate and glutamate from the dorsal spinal cord [139].

Recent research has shown that CGRP in the spinal cord is not only derived from primary afferents but also from a distinct group of excitatory interneurons in the spinal cord dorsal horn and TNC [140]. Under resting conditions, CGRP interneurons are regulated by tonic inhibitory control. However, stimulating the dorsal roots through electrical activation of non-nociceptive Aβ fibers (large myelinated afferents) led to depolarization of these neurons. Additionally, chemogenetic activation of CGRP interneurons resulted in mechanical hypersensitivity. Based on this finding the authors suggested that, under certain conditions, CGRP interneurons become hyperexcitable and may contribute to either ascending pathways from the deep dorsal horn or to reflex circuits [140]. This matter needs more investigation in regard to migraine pathophysiology.

Additionally, CGRP sensitizes neurons to glutamate by increasing the density of glutamate receptors, including NMDA and AMPA receptors. Studies indicate that applying CGRP to dorsal horn neurons can alter their membrane potential [141], leading to an increase in spontaneous discharges as well as discharges triggered by intracellular depolarizing pulses [141, 142]. This heightened excitability in the neuronal membrane could, therefore, increase firing in response to NMDA and AMPA application. However, it is worth noting that in the Ebersberger study, they did not observe neuron firing induced solely by CGRP, which implies that any depolarization effect from CGRP might have been minimal, if present at all [143]. Another possible scenario is that CGRP increases Ca^{2+} uptake in depolarized synaptosomes [144], which may, in turn, trigger the release of glutamate [145, 146]. This CGRP-driven increase in glutamate within the tissue could cause neuronal depolarization, potentially amplifying their responsiveness to externally applied NMDA and AMPA.

Potential feedback loop

Based on the evidence reviewed, it appears that elevated glutamate levels lead to the release of CGRP, especially in the brainstem. This release, in turn, increases both glutamate release and the sensitivity of its receptors. This creates a cyclical interaction where glutamate and CGRP enhance each other's effects, resulting in a sustained state of neuronal excitation and sensitization (Fig. 2).

Role of glutamate and CGRP in development of peripheral sensitization

Peripheral sensitization related to migraine refers to a lowered activation threshold and an amplified response of sensory nerves in meninges and TG to external stimuli [147]. This is characterized by enhanced stimulus-dependent pain, known as primary hyperalgesia which is clinically evident where the headache worsens with coughing or physical activity, and through the characteristic throbbing or pulsating nature of migraine headache [148].

Glutamate's role in peripheral sensitization

Peripheral sensitization typically occurs following peripheral nerve injury or inflammation [149]. Both of these conditions have been shown to cause an increased release of glutamate in the TG neurons [150, 151]. Glutamate can enhance inflammation at the peripheral level by directly affecting satellite glial cells [152]. These cells, which surround the cell bodies of neurons in the TG, release substances that can affect adjacent neurons, potentially altering their excitability [153]. These satellite glial cells have been shown to also release glutamate themselves, including during nociceptive signaling [152]. Depolarization of these glial cells triggers the vesicular release of glutamate, which can diffuse and influence TG neurons [152]. Activation of type C fibers in the TG

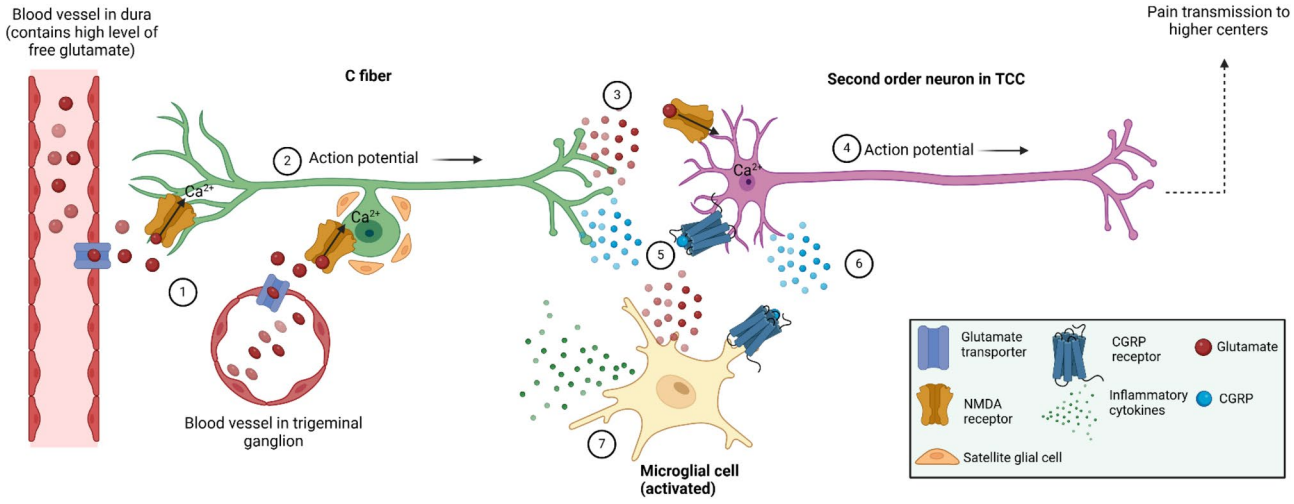

Fig. 2 Interaction Between Glutamate and CGRP Influenced by Peripheral Glutamate. (**1**) High levels of glutamate in the dura or blood vessels of the TG can more easily enter the brain due to the lack of BBB protection in these areas. (**2**) This glutamate binds to NMDA, AMPA, or kainate receptors at the peripheral side (only NMDA is shown in the figure), increasing Ca^{2+} influx and activating primary afferent neurons. (**3**) The signal is transmitted to second-order neurons in the TCC of the brainstem through glutamate released from the central end into the synaptic cleft. (**4**) The excitatory signal then propagates to higher brain regions involved in pain processing, such as the thalamus. (**5**) In addition to glutamate, CGRP is released from the central terminals of primary C fibers and activates its receptors on second-order neurons. (**6**) Activated second-order neurons release CGRP, which stimulates its receptors on nearby microglial cells. (**7**) Microglial cells, in response to CGRP receptor activation, release additional glutamate and inflammatory cytokines. This glutamate ensures the activation of second-order neurons and amplifies sensitization. *TG: trigeminal ganglion*, *BBB: blood brain barrier*, *Ca^{2+}: calcium*, *TCC: trigeminal cervical complex. CGRP: calcitonin gene-related peptide*, *NMDA: N-methyl-D-aspartic acid*, *AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid*, Created in https://BioRender.com

leads to the release of CGRP [40]. The satellite glial cells contain CGRP receptors and can respond to CGRP by further releasing glutamate and inflammatory cytokines [154]. This process ensures the sustained release of glutamate and CGRP, contributing to peripheral sensitization. It is also important to note that exogenous administration of monosodium glutamate (MSG) can similarly activate the TG [154], which may help explain the common report from migraineurs of sensitivity to MSG as a dietary trigger for migraine [155–157].

CGRP's role in peripheral sensitization

As mentioned earlier, CGRP alone may not directly trigger nociception, but evidence supports CGRP's role in peripheral sensitization. For instance, repeated injections of low doses of CGRP into rat paws induced peripheral sensitization, as evidenced by a significant decrease in the response threshold to noxious mechanical stimuli [158]. In another study, injection of a CGRP receptor antagonist prevented the behavioral signs of hyperalgesia in rats with peripheral nerve injury [32]. Nerve damage or inflammation in the periphery leads to the localized release of proinflammatory mediators such as bradykinin, histamine, chemokines, cytokines, and glutamate [159]. These substances can sensitize peripheral nociceptors by lowering their activation threshold or directly triggering action potentials, thereby activating them. Persistent activation of the nociceptors over time, causes translational changes including- but not limited to- an increase in the production of SP and CGRP, thus maintaining a state of peripheral sensitization [159].

In animal models of migraine, it is well-established that SP and CGRP induce neurogenic inflammation, characterized by vasodilation, plasma protein extravasation (from leaky blood vessels), and mast cell degranulation. This mechanism is a key piece of evidence supporting the involvement of CGRP in migraine pathophysiology. However, some findings in humans cannot be overlooked. In an attempt to explore the acute effects of neuropeptides on human skin, SP induced both vasodilation and plasma protein extravasation, while CGRP caused potent vasodilation without triggering plasma extravasation [160]. In another study, intense electrical stimulation of cutaneous nerves in human volunteers, which triggered the release of SP and CGRP, failed to induce mast cell degranulation, histamine release, or plasma protein extravasation [161]. It should be noted that research on SP has primarily focused on a single receptor pathway (neurokinin-1) [162]. However, it is possible that SP may also act through other receptors, contributing to neurogenic inflammation and, consequently, migraine. Overall, the role of neurogenic inflammation in migraine pathophysiology is well-supported, particularly in animal models (as detailed in the review by Spekker et al. [163]); However, further clinical studies are needed to fully validate this theory in clinical models.

On the other hand, the release of inflammatory cytokines as a result of these mediators can lead to BBB permeability [164]. There is also evidence that SP, as mentioned earlier, can also cause a temporary disruption in BBB integrity in in vitro studies [135]. Compromising the BBB could be an example of how peripheral sensitization can start transitioning into central sensitization.

Role of glutamate and CGRP in development of central sensitization

Central sensitization happens after peripheral sensitization and is thought to be the underlying mechanism of chronic migraine; clinically presenting as allodynia [165]. Allodynia occurs when a typically non-painful stimulus triggers pain, with sensitivity extending beyond the original pain location [166, 167]. Around 80% of migraine sufferers develop cutaneous allodynia [168, 169]. Central sensitization differs from peripheral sensitization by involving hyperexcitability of second-order neurons in the trigeminocervical complex or higher-order neurons in the thalamus, even in non-inflamed tissues [170].

Glutamate's role in central sensitization

Central sensitization is believed to be mainly driven by the increased activation of NMDA glutamate receptors on higher-order neurons [171]. Studies have indicated that administering glutamate or its receptor agonists induces allodynia and hyperalgesia [172, 173]. Conversely, blocking glutamate counteracts these nociceptive effects [174, 175]. In normal situations, magnesium (Mg^{2+}) serves as a block of the NMDA receptor. When nociceptor-evoked synaptic potentials accumulate, they cause membrane depolarization, which removes the voltage-dependent Mg^{2+} block from NMDA channels, allowing Ca^{2+} to enter the cell [176]. This influx of Ca^{2+} activates intracellular kinases, triggering post-translational modifications, particularly the phosphorylation of membrane receptors and ion channels. As a result, there is an increase in neuronal excitability, which makes the neurons more sensitive to inputs that would usually fall below the threshold for activation, particularly those caused by low-intensity stimuli. Consequently, central sensitization occurs [30]. The activation of group I mGluRs by glutamate also plays a significant role in the development of central sensitization. While these receptors are not involved in baseline nociception [177, 178], their activation is crucial for the activity-dependent central sensitization driven by C-fiber activity [179–181].

In addition to the upregulation of glutamate receptors in the development of central sensitization, impaired clearance of glutamate at the synapse between primary and secondary neurons in the brainstem has also been proposed. In healthy synapses, nearly all released glutamate in the synaptic cleft is taken up by astrocytes through excitatory amino acid transporters (EAATs) [73]. Within these astrocytes, glutamate is converted into glutamine, and then released in this non-toxic form to neurons, where it can be taken up and converted back into glutamate for repeated use [73]. In an animal model of chronic migraine, downregulation of EAAT2 transporters in the TNC has been observed [182]. This would limit the clearance of glutamate from the synaptic cleft, thereby causing overexcitation which could contribute to central sensitization. In contrast, up-regulation of these transporters has been shown to alleviate central sensitization in a rat model of chronic migraine [182].

If presynaptic neurons release a high amount of glutamate, and astrocytes fail to clear it from the synaptic cleft, it can lead to excitotoxicity. Excitotoxicity refers to repetitive neuronal excitation that causes neuronal damage and ultimately cell death [73]. In neurons, overactivation of glutamate receptors leads to excessive production of free radicals by mitochondria. Once the production of free radicals exceeds the cell's antioxidant defense capacity, oxidative stress occurs [183]. On the other hand, nearby microglial cells, which express NMDA and mGlu receptors, can be directly triggered by glutamate to release inflammatory mediators [184], leading to neuroinflammation. This creates the neurotoxic triad of excitotoxicity, oxidative stress, and neuroinflammation—each capable of inducing and perpetuating the other two states. This triad has been proposed as an underlying mechanism implicated in neurological disorders, including migraine [185], which has also been associated with central sensitization (Fig. 3). One proposed mechanism involves the enhancement of NMDA receptor phosphorylation by reactive oxygen species (ROS), driving central sensitization [186, 187]. Phosphorylation of AMPA and NMDA receptors enhances their activity and density, resulting in postsynaptic hyperexcitability [188, 189]. Additionally, neuroinflammation, mediated by activated microglia, plays a significant role in the development of central sensitization. Proinflammatory cytokines and chemokines released by microglia affect both presynaptic and postsynaptic neurons [190]. Presynaptically, they enhance glutamate release, while postsynaptically, they positively modulate NMDA and AMPA receptors. For instance, interleukin-1 beta (IL-1β) increases excitatory transmission through NMDA receptor phosphorylation and reduces inhibitory signaling mediated by gamma-aminobutyric acid (GABA) and glycine [191]. Similarly, tumor necrosis factor alpha (TNF-α), also produced by microglia, binds to postsynaptic receptors in second-order neurons, amplifying NMDA and AMPA receptor responses [192, 193].

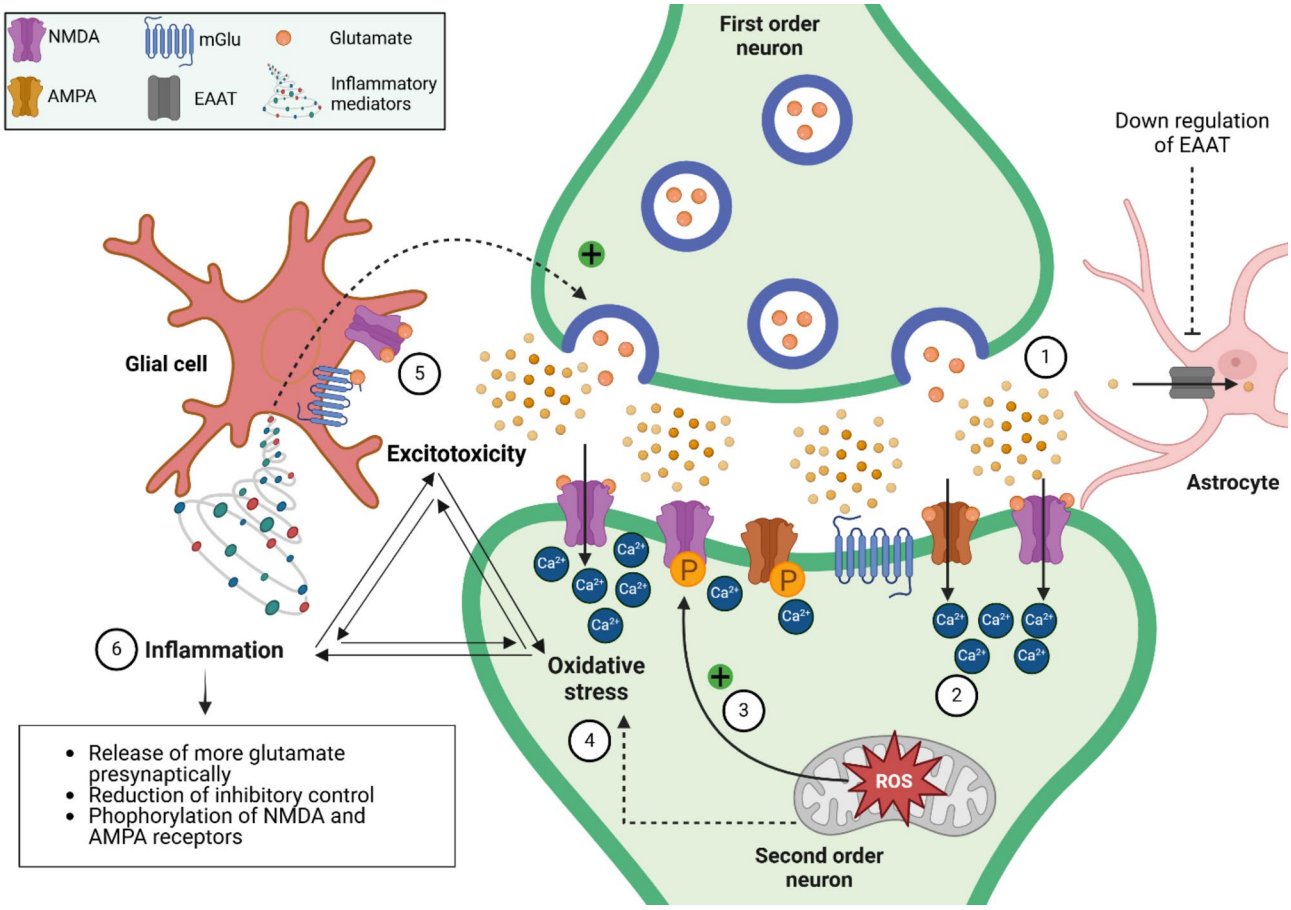

Fig. 3 Central Sensitization Model Induced by the Neurotoxic Triad. (**1**) Excessive glutamate release and reduced reuptake of glutamate by astrocytes (through EAAT) leads to excitotoxicity, triggering massive Ca^{2+} influx in second-order neurons, mainly through NMDA receptors. (**2**) This eventually leads to the production of ROS by mitochondria. (**3**) ROS enhances NMDA receptor phosphorylation, driving central sensitization. (**4**) High levels of ROS surpass the cell's antioxidant capacity causing oxidative stress in second-order neurons. (**5**) Available glutamate in the synaptic cleft can activate its NMDA and mGlu receptors on nearby microglial cells. (**6**) In response, microglial cells release inflammatory mediators that increase glutamate release presynaptically, enhance NMDA and AMPA receptor activity postsynaptically (through phosphorylation), and suppress inhibitory GABA and glycine signaling, further amplifying sensitization. These interconnected events form a triad of excitotoxicity, oxidative stress, and neuroinflammation, which not only potentiate central sensitization but also sustain it. *NMDA: N-methyl-D-aspartic acid*, *AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid*, *mGluRs: Metabotropic glutamate receptors*, *EAAT: Excitatory amino acid transporters*, *ROS: Reactive oxygen species. Ca^{2+}: calcium*, *GABA: gamma-aminobutyric acid.* Created in https://BioRender.com

CGRP's role in central sensitization

CGRP participates in central sensitization through postsynaptic CGRP receptors. Activation of CGRP receptors in the spinal cord leads to mechanical hyperalgesia and increases the sensitivity of dorsal horn neurons in rats [31]. One potential mechanism for heightened sensitivity could be an increase in the number of CGRP receptors. In an animal study, injection of CGRP elevated sensitivity to mechanical stimuli in mice. Notably, this effect was even more pronounced in mice with increased expression of the CGRP receptor subunit [194]. Additionally, CGRP potentiates central sensitization through the activation of some kinase enzymes involved in triggering prolonged increases in gene transcription [195, 196]. CGRP has been found to enhance the release of SP and glutamate from rat spinal dorsal horn neurons during mechanical nociception [146]. These findings suggest that, although CGRP plays a central role in sensitization, part of its effects may be mediated indirectly through SP and glutamate.

While both glutamate and CGRP play key roles in central sensitization, their effects could be different in nature and dimension. In a study by Khodorova et al., they used subcutaneous injection of endothelin-1 (a potent vasoconstrictor) in rats in an in vivo model [197]. Subcutaneous injection of endothelin-1 into the hind paw of rodents results in local nociceptive sensitization or hyperalgesia [198, 199]. In this study, the initial rise in endothelin-1-induced mechanical allodynia, which remains unchanged by CGRP receptor antagonists, suggests that mediators released upon endothelin receptor activation may be involved in developing allodynia. They

propose that glutamate, present in primary afferent neuron axons, and released in peripheral tissues following nerve stimulation, might also be released in the skin via neuronal endothelin receptor activation. This release of glutamate could subsequently stimulate a group of small-diameter, peptide-containing neurons, prompting the release of CGRP and possibly other peptides. Their findings indicate that blocking local NMDA receptors almost completely eliminates mechanical allodynia caused by endothelin-1. Interestingly, co-injection of NMDA receptor antagonists with endothelin-1 also prevented allodynia. In contrast, co-injection of the CGRP antagonist attenuated only the later phase of allodynia (> 30 min). This suggests that CGRP might play a role in maintaining, rather than initiating, the mechanisms of sensitization. However, it is important to note that evidence supporting the hyperalgesic effect of endothelin-1 and its subsequent mechanisms is derived from animal models, and its extrapolation to humans should be approached with caution [200].

Therapeutic potential and challenges in targeting glutamate and CGRP

NMDA receptor antagonists have been studied for their potential to treat and prevent migraine. This includes drugs like ketamine, which directly blocks the NMDA receptor; and medications like memantine, which is a partial antagonist to the NMDA receptor but with lower affinity than ketamine [201, 202]. A recent meta-analysis that included 38 clinical trials, compared memantine efficacy with the guideline-recommended prophylactic agents for migraine, including anti-CGRP monoclonal antibodies [202]. They showed that among all the interventions studied, memantine showed the second-largest decrease in migraine days and achieved the highest 50% response rate [202].

CNS side effects associated with glutamate antagonists have limited the enthusiasm for their use in migraine treatment [203]. Given that glutamate is a key neurotransmitter in the brain, altering its signaling is likely to result in CNS-related side effects. Modulating glutamate pathways can lead to adverse psychotomimetic effects such as hallucinations, delusions, paranoia, delirium, and impairments in learning, memory, and motor control [204]. Reported side effects of memantine (as a preventive option in migraine patients) include agitation, confusion, dizziness, weight loss, fatigue, rash, somnolence, weakness, anxiety, and depression [205, 206]. For ketamine, side effects such as dissociation, sedation, and blood pressure changes have been observed [207–209]. Frequent use of ketamine is linked to neurocognitive impairment, especially working and episodic memory deficits [210]. The very effects which have restricted ketamine's clinical use, have also made it attractive to recreational users. Ketamine is highly addictive, being known on the street as 'Special K' [211]. On the other hand, to date, there have been no head-to-head studies of glutamate receptor antagonists with anti-CGRP medications, so most comparisons have been based on indirect estimates and have involved small sample sizes. Since glutamate is not only present endogenously in the brain, but is also found in the diet, with free forms of glutamate and aspartate (dietary excitotoxins that activate NMDA receptors) being commonly found as food additives [212], there is also increasing interest in the idea of dietary modulation as a potential treatment for migraine [213].

As stated above, there is great interest in the use of anti-CGRP monoclonal antibodies for migraine treatment. These work by blocking the CGRP pathway and represent the first preventive treatments specifically developed for migraine, with generally favorable safety profiles [214–218]. Later studies have validated their effectiveness, even in patients who were resistant to other treatments [219–221].

Based on published data so far, around one-third of patients show a strong response to anti-CGRP monoclonal antibodies, while another third does not respond at all [8–11]. Some potential explanations exist for the non-responders to anti-CGRP medication. The first pertains to chronic migraineurs whose attacks are predominantly driven by central mechanisms, rendering anti-CGRP medications less effective. The second explanation is rooted in anatomical evidence indicating a lack of co-localization between CGRP and its receptors [105]. Specifically, C fibers contain CGRP, while Aδ fibers house CGRP receptors. For example, studies show that fremanezumab, a CGRP antagonist, inhibits Aδ fibers, but not C fibers [222]. At the peripheral level, either in episodic or chronic migraine, antagonizing CGRP or its receptors may inhibit Aδ fiber activation. However, C fibers can still be activated through other mechanisms, such as cortical spreading depression and inflammation [222, 223].

Some limitations of anti-CGRP medications include their high cost and a lack of long-term data from randomized trials. Notably, these newly developed medications are still unavailable in many countries. In fact, a recent survey by the international headache society across 84 countries reported that new migraine treatments, such as rimegepant and erenumab (both CGRP receptor antagonists), remain largely inaccessible across Latin America, Asia, and Africa [224]. As a result, these treatments were initially recommended as second or third-line options for chronic migraine, though more recent guidelines have endorsed them as first-line therapies [225, 226].

Notably, the issue extends beyond non-responders. While this family of medications is generally safe, some patients experience unavoidable side effects. These impact multiple organs and systems, including the

gastrointestinal, cardiovascular, nervous, respiratory, immune, and musculoskeletal systems, as well as issues with the skin and hair. Some examples of these side effects include constipation, hypertension, palpitations, anxiety, vertigo/dizziness, paresthesia, insomnia, flu-like symptoms, hypersensitivity reactions, myalgia, and alopecia [227–230]. Such adverse effects can diminish patients' enthusiasm for this treatment. Moreover, since these medications are newly developed, limited data is available about their long-term safety. A recent observational study revealed that during a 1.5-year follow-up, 1.6% of patients receiving anti-CGRP medications experienced moderate to severe cardiovascular events despite having no cardiovascular risk factors or hypertension at baseline [231]. These medications are also contraindicated during pregnancy and lactation, as well as in individuals with vascular disorders or ischemia [12–16], which limits their use in certain populations.

Clinical implications: the role of external triggers

Extensive reports exist regarding the role of triggers in migraine [232–234]. It is important to note here that a reported migraine trigger may sometimes be confused with symptoms of the premonitory phase, which is already part of the migraine attack process [235]. Based on this notion, it has been suggested that studies investigating "migraine" and its "triggers" should carefully assess the specific stages of the migraine cycle, considering not only the end of the previous attack, but also the onset of the next one [235]. In addition to this important caveat, it is also important that future research examine the potential mechanisms for how a specific exposure may affect key aspects of migraine, such as effects on CGRP, glutamate, and vasodilation. One common argument against certain substances having the ability to affect migraine is that the BBB protects the brain from chemicals in the blood. Two key considerations challenge this. First, as mentioned earlier, not everyone has an intact BBB capable of fully shielding against toxins and triggers. Although evidence remains inconclusive regarding BBB permeability in migraine patients, it is suggested that the barrier may become transiently permeable during an attack [236]. Second, and crucially, if migraine pain begins with the activation of primary afferents in the dura, we must acknowledge that the TG and dura are outside the BBB's protection. Therefore, these critical regions for the formation of pain signals are vulnerable to external triggers circulating in the blood. This provides a great opportunity to develop targeted prevention and intervention strategies. In this regard, a non-pharmaceutical approach that controls the peripheral level of glutamate could be a valuable alternative option for preventing attacks.

Monosodium glutamate (MSG) is recognized as the third most common dietary trigger for headaches [237–240]. Studies have shown that consuming 150 mg/kg of MSG can lead to increased reports of headache, nausea, and vomiting [237–240] - symptoms commonly linked to acute migraine attacks. In individuals with fibromyalgia, lowering dietary MSG intake has also been associated with reduced musculoskeletal pain and reduced headache occurrence [241]. Using a glutamate-selective biosensor, glutamate levels were measured in the TG of an anesthetized male rat before and after a dose of MSG [242]. At time zero, MSG was injected into the carotid artery, resulting in a sustained rise in glutamate levels in the TG. Then, these afferents activated second-order neurons in the brain stem nuclei, and, finally, higher areas involved in pain perception of the brain. This aligns with earlier observations that MSG, when applied peripherally, enhances the ongoing spiking activity in brainstem neurons [25]. As free glutamate (not-bound to a protein) is found as a naturally occurring amino acid in some foods, and is also widely used in the food industry as a flavor-enhancing food additive, diet serves as an important source of exogenous glutamate in blood [212, 243, 244].

Interestingly, diet may also play an important protective role against migraine, as magnesium and several other nutrients have shown efficacy in combating glutamate excitotoxicity, inflammation, and oxidative stress, with promising results in clinical trials involving migraine patients (as detailed in our previous review [213]). Additionally, some studies indicate that specific dietary factors may also influence circulating CGRP levels, with a potential impact on migraine outcomes (reviewed in [245]). Therefore, future research is needed to fully understand how diet may be influencing migraine through effects on glutamate and CGRP, and whether dietary interventions targeting these neuro-messengers may have anti-migraine effects.

What have we learned about CGRP-glutamate dynamics, and what remains unknown?

As discussed in this review, migraine originates peripherally and progresses centrally, reaching a point in chronic migraine where it may become entirely centralized. Anti-CGRP therapies primarily target peripheral pain mechanisms, such as neurogenic inflammation and vasodilation, but central mechanisms also play a significant role in migraine. In some patients, central mechanisms may be more dominant than peripheral ones, meaning that targeting CGRP alone may not be enough to address the central components of their migraines, such as glutamate-mediated excitotoxicity. This hypothesis is backed up by evidence showing that the presence of central sensitization and its associated symptoms were particularly predictive of treatment failure. In this regard, allodynia is predictive of a poor response to anti-CGRP medications

[246]. Since allodynia arises from central sensitization, these treatments may not be sufficient to reverse chronic migraine once central sensitization is established. The central role of glutamate in higher regions of the pain pathways is well-supported [81, 82], making it logical to hypothesize that certain patients may benefit more from targeting glutamate. This may also apply to migraineurs with aura. Cortical spreading depression, the neural phenomenon underlying aura, occurs within the brain itself, indicating that aura symptoms originate from the central nervous system. The involvement of glutamate in mediating cortical spreading depression through NMDA receptors is widely supported [247, 248]. Therefore, it is reasonable to hypothesize that this migraine subtype may be particularly responsive to glutamate-targeted interventions.

The mechanisms discussed in this paper highlight the complexity of migraine and the variability in its clinical presentation across patients. Each mechanism may contribute to migraine pathophysiology and should not be considered in isolation. Instead, a comprehensive view that integrates these diverse processes is needed. Accordingly, the development of varied treatment strategies is essential. Future research should focus on therapies that target both peripheral and central components to more effectively address the full spectrum of migraine pathophysiology.

Conclusion

The evidence supports a model in which glutamate plays an upstream role in stimulating CGRP release, while CGRP, in turn, enhances glutamate signaling, creating a feedback loop that may contribute to sustained pain in migraine. With growing recognition of glutamate's role in both peripheral and central sensitization, targeting glutamate pathways presents a promising therapeutic avenue—particularly for individuals who do not respond to CGRP-based treatments. On the other hand, given the involvement of multiple underlying mechanisms and the limitations and challenges associated with current therapies, it is logical to adopt diverse approaches to effectively treat migraine. Furthermore, as evidence continues to support migraine initiation at the dura and TG, future research should explore strategies to reduce peripheral glutamate exposure.

Abbreviations

CGRP	Calcitonin gene-related peptide
BBB	Blood-brain barrier
TG	Trigeminal ganglion
TNC	Trigeminal nucleus caudalis
TCC	Trigeminal cervical complex
CNS	Central nervous system
iGluRs	Ionotropic glutamate receptors
mGluRs	Metabotropic glutamate receptors
NMDA	N-methyl-D-aspartic acid
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Ca^{2+}	Calcium
NO	Nitric oxide
cGMP	Cyclic guanosine monophosphate
cAMP	Cyclic adenosine monophosphate
MSG	Monosodium glutamate
SP	Substance P
Mg^{2+}	Magnesium
EAATs	Excitatory amino acid transporters
ROS	Reactive oxygen species
IL-1β	Interleukin-1 beta
GABA	Gamma-aminobutyric acid
TNF-α	Tumor necrosis factor-alpha

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