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The vessel-to-neuron trigeminovascular hypothesis of migraine pathogenesis – the 'pro' argument

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Abstract

Purpose The pathogenesis of migraine remains incompletely understood, with traditional theories oscillating between purely vascular or strictly neuronal concepts. However, emerging evidence points to a more integrated "vessel-to-neuron" mechanism. This debate paper explores the role of intracranial vasculature in initiating migraine pain, offering a unifying concept that reconciles these traditionally divergent views.

Findings Neurosurgical findings confirm that stimulating or mechanically distending intracranial arteries can elicit migraine-like pain, suggesting that these vessels might serve as substrates for migraine pathogenesis. Activation of the trigeminovascular system and subsequent release of migraine-inducing neuropeptides lead to neurogenic inflammation within the meninges, promoting both vasodilation and the sensitization of meningeal nociceptors. Interestingly, all identified molecular migraine triggers potently dilate the intracranial vasculature, converging on potassium efflux from vascular smooth muscle cells. This efflux likely modifies local chemical gradients, thereby depolarizing trigeminal afferents and driving the cascade of ascending nociceptive signaling. Therapeutic interventions further reinforce the causal role of vascular contributions to migraine pathogenesis. Blocking vasodilatory neuropeptides or constricting extracerebral arteries effectively prevents and terminates migraine attacks, underscoring the importance of peripheral mechanisms. More than mere vasodilation, this hypothesis posits that chemical agents, including potassium released by vascular smooth muscle cells, might precipitate migraine onset. The resulting mechano-chemical stimulus might activate perivascular nociceptors and ascending trigeminal pain signaling, ultimately culminating in generation of a migraine attack.

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Introduction

Migraine is a prevalent and disabling neurological disorder characterized by recurrent attacks of moderate to severe headache, often accompanied by photophobia, phonophobia, nausea, and vomiting [1, 2]. About one-third of people with migraine experience aura—transient neurological disturbances, most commonly visual, that precede or accompany the headache [3]. Despite extensive research, the precise mechanisms underlying migraine pathogenesis remain incompletely understood [2]. Traditional views have oscillated between vascular and neuronal hypotheses [4, 5], but emerging evidence stresses the need for a more integrated concept.

In the mid-20th century, Harold G. Wolff proposed the vascular hypothesis, suggesting that migraine arises from intracranial vasodilation leading to headache [6]. This theory was, in part, based on the throbbing quality of migraine pain and observations that vasoconstrictive agents provided relief [6, 7]. While influential, the vascular hypothesis faced limitations, as it could not fully explain the plethora of neurological symptoms associated with migraine.

Subsequent research shifted focus toward neuronal mechanisms [5]. One prominent theory involves cortical spreading depression (CSD), a wave of neuronal and glial depolarization propagating across the cerebral cortex, associated with migraine aura [8]. Alternative neuronal hypotheses propose that migraine attacks result from functional oscillations within the brain stem or hypothalamus, affecting pain modulation pathways [9, 10]. These concepts highlight the role of neuronal hyperexcitability and neurotransmitter imbalances [5]. Yet, they often lack convincing explanations for the peripheral symptoms of migraine and the efficacy of peripherally acting treatments.

In 1979, Moskowitz and colleagues introduced the trigeminovascular hypothesis, providing a more compelling framework [11]. This hypothesis posits that activation of the trigeminovascular system (TVS) is central to the pathogenesis of migraine pain [11]. The TVS comprises the trigeminal nerve and its axonal projections to intracranial blood vessels and the meninges [12]. The release of vasoactive signaling molecules, such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP), leads to neurogenic inflammation, intracranial vasodilation, and sensitization of meningeal nociceptors [12]. Importantly, the trigeminovascular hypothesis views intracranial vasodilation not as a primary cause but as a consequence of neurogenic inflammation and nociceptor activation [11]. The vasodilation is thus considered a surrogate marker rather than a direct initiator of migraine pain.

Building on these concepts, the vessel-to-neuron trigeminovascular hypothesis integrates vascular changes and neuronal activation within the TVS, proposing that intracranial vasodilation can directly initiate migraine attacks through activation of meningeal nociceptors [2]. This hypothesis suggests that mechanical and chemical stimuli resulting from intracranial vasodilation activate perivascular trigeminal and upper cervical nerve endings, leading to the release of signaling molecules that mediate migraine pathogenesis.

By considering intracranial vasodilation as both a cause and an effect within the migraine cascade, this hypothesis provides a unified model that accounts for clinical observations, experimental evidence, and therapeutic advents. The purpose of this review is to introduce and discuss the vessel-to-neuron trigeminovascular hypothesis, summarizing current evidence, and discussing its implications for migraine research.

The trigeminovascular system: anatomical and physiological foundations of migraine

The pathogenesis of migraine is intricately linked to the anatomy and physiology of the TVS [12]. Understanding this system provides fundamental insights into how vascular changes might directly influence nociceptor activity, leading to migraine attacks.

Intracranial vasculature and innervation

The intracranial vasculature, particularly the meningeal arteries, is densely innervated by nociceptive fibers originating from both the trigeminal nerve and upper cervical spinal nerves (C1-C3) [13–15]. These fibers lie in close proximity to blood vessels, positioning them ideally to detect and respond to vascular changes [16]. The convergence of trigeminal and upper cervical afferents in the trigeminocervical complex (TCC) facilitates bidirectional communication and cross-sensitization, contributing to the manifestation of headache and the often-associated neck pain in migraine [13, 14]. From the second-order neurons in the TCC, nociceptive signals are relayed to third-order neurons within the thalamus, which then project to the somatosensory cortex, insula, and other brain regions, culminating in the perception of migraine pain [12, 17].

Nociceptors and receptors

Meningeal nociceptors primarily comprise unmyelinated C fibers and thinly myelinated Aδ fibers, which detect noxious stimuli and express a variety of receptors and ion channels [18]. Key among these are transient receptor potential (TRP) channels, which respond to thermal and chemical stimuli [19]. In addition, mechanosensitive Piezo channels detect mechanical stretch and deformation of the cellular membrane [20]. The presence of these channels enables meningeal nociceptors to respond to a

wide array of stimuli, including chemical, and mechanical changes associated with vascular dynamics.

Preclinical studies have demonstrated that exposure to migraine-triggering agents sensitizes meningeal nociceptors to mechanical stimuli [15, 21, 22]. As a result of this sensitization, these nociceptors exhibit an exaggerated response to mechanical stimuli [15, 21–23], possibly contributing to the throbbing nature of migraine pain and its exacerbation during routine physical activity. This phenomenon is further underscored by the resemblance of symptoms between meningeal irritation—such as that observed in meningitis—and migraine [24], highlighting the pivotal role of meningeal nociceptors in migraine pathophysiology.

Classical and contemporary neurosurgical studies have provided empirical support for the role of intracranial vasculature in migraine pathogenesis [6, 25, 26]. Pain-sensitive intracranial structures, including the meninges and its blood vessels, have been identified, whereas the brain parenchyma itself is largely insensitive to pain [27]. In awake patients undergoing neurosurgical procedures, direct stimulation of perivascular meningeal sites elicits headache ipsilateral to the stimulus [6, 25]. The patients described this headache as deep and aching, accompanied by nausea—symptoms that closely mirror those experienced during migraine attacks [6, 25]. Furthermore, mechanical distension of intracranial arteries induces throbbing pain that ceases almost immediately upon the cessation of the distension [26]. These clinical observations suggest how vessel-to-neuron signaling might contribute directly to migraine pain.

Mechanisms of vessel-to-neuron signaling

Causality in migraine does not necessitate that a factor is either sufficient or necessary to trigger an attack in all instances. Analogous to how smoking is a major cause of lung cancer without being the sole determinant, vessel-to-neuron signals might causally contribute to migraine attacks even though exceptions exist. The role of the intracranial vasculature in migraine is more nuanced than simple mechanical vasodilation; it involves both chemical and mechanical signals originating from vascular smooth muscle cells (VSMCs) within the walls of intracranial arteries [2, 28].

Mechanical and chemical activation of meningeal nociceptors

Intracranial vasodilation results in vessel distension, which mechanically might activate adjacent meningeal nociceptors. Mechanosensitive ion channels, such as Piezo, respond to membrane stretch and transduce mechanical forces into electrical signals [29, 30]. Upon activation, these channels facilitate the influx of cations, leading to depolarization of nociceptors and initiation of action potentials that propagate along the trigeminal pain pathway [20]. Ample evidence also implicates other mechanosensitive channels in migraine, including K2P channels and potentially also NMDA receptors [28], which recent findings suggest might possess mechanotransducive properties [31]. Yet other receptors modulate mechanosensitivity, including multiple members of the TRP and ASICs families that respond to noxious stimuli [28]. The aforementioned clinical observations support these mechanisms; distension of intracranial arteries during neurosurgical procedures trigger migraine-like pain in awake patients [6, 25, 26]. This direct activation underscores the potential for vascular distension to initiate nociceptive signaling.

Vasodilation is also associated with the opening of ATP-sensitive potassium (K_{ATP}) channels and large conductance calcium-activated potassium (BK_{Ca}) channels within the VSMCs [32, 33]. The activation of these channels leads to potassium efflux from VSMCs, increasing the extracellular potassium concentration in the perivascular space. Elevated extracellular potassium reduces the membrane potential threshold of nearby nociceptors, facilitating their depolarization and activation [34]. Recent evidence provides mechanistic support for this line of reasoning. Opening of K_{ATP}channels with levcromakalim infusion activated ~ 70% of mechanosensitive meningeal nociceptors – the neurons considered responsible for migraine headache [35]. This was demonstrated in a study using direct, in-vivo single-unit electrophysiology recording from the trigeminal ganglion in rats, while relying on a design that closely mimicked human provocation studies [35]. This finding likely explains experimental studies demonstrating that pharmacological openers of potassium channels, including K_{ATP} channels and BK_{Ca}channels, can trigger migraine attacks in people with migraine [36, 37]. Conversely, blocking these channels attenuates pain responses in preclinical models [38].

During vasodilation, endothelial cells and VSMCs release various signaling molecules, including nitric oxide (NO) and prostaglandins [39, 40]. These mediators are known triggers of migraine attacks and potent dilators of intracranial arteries in people with migraine [41–43]. Furthermore, NO can enhance TRP channel activity, while prostaglandins lower the activation threshold of nociceptors [22]. The release of these substances can thus contribute to amplifying pain signals within the TVS system.

Collectively, these mechanical and chemical signals are interrelated and might act synergistically to activate perivascular nociceptors. Experimental disentanglement is challenging, but both pathways provide plausible mechanisms for vessel-to-neuron signaling in migraine pathogenesis.

Neurogenic inflammation and feedback loops

Neurogenic inflammation represents a pivotal mechanism in migraine pathogenesis, driven primarily by the activation of perivascular meningeal nociceptors [44]. Once activated, these nociceptors release a host of vasodilatory and pronociceptive substances, including CGRP, PACAP, and substance P [45, 46]. Collectively, these neuropeptides induce vasodilation, increase vascular permeability, and sensitize nociceptors to subsequent stimuli.

Concurrently, perivascular immune cells such as macrophages and mast cells can be activated by these neuropeptides, leading to the additional release of prostaglandins, histamine, and other pro-inflammatory mediators [47–50]. These agents further expand the inflammatory milieu by promoting vasodilation and enhancing nociceptor excitability, thereby contributing to migraine initiation and progression [22]. In this manner, a composite response emerges in which VSMCs, immune cells, and nociceptors interact reciprocally to sustain and amplify both vasodilation and nociceptor activity.

This process fosters a positive feedback loop wherein the recruitment of additional nociceptors perpetuates the neurogenic inflammatory response, causing it to intensify over time [4]. As a result, migraine headache may become self-sustaining, with increasing numbers of activated nociceptors releasing growing concentrations of pro-inflammatory and pro-nociceptive mediators. By augmenting vasodilation and lowering nociceptor activation thresholds, this loop underscores the importance of vessel-to-neuron signaling in both the initiation and maintenance of migraine.

Emerging evidence supporting a causal role of intracranial vasodilation

Migraine provocation models

Pharmacological agents that cause dilation of intracranial arteries have been shown to induce migraine attacks in people with migraine. Notably, a 20-minute continuous intravenous administration of CGRP, NO donors (e.g., nitroglycerin), and PACAP triggers migraine attacks in people with migraine but not in healthy adults [51]. This specificity supports the causal role of intracranial arterial dilation and vessel-to-neuron signaling in migraine pathogenesis, as the same dose and infusion duration of these molecules do not elicit similar responses in healthy adults.

This approach implicates specific molecular targets in migraine pathogenesis and allows for the study of induced migraine attacks akin to spontaneous ones. Identification of molecular migraine triggers identified through randomized, double-blinded, placebo-controlled, crossover trials represent a gold standard for establishing causality in medical research. These models have been instrumental in demonstrating the role of endogenous neuropeptides (e.g., CGRP, NO, and PACAP) and intracellular signaling pathways involving cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in migraine [52].

Vascular effects of molecular migraine triggers

All identified molecular migraine triggers dilate cephalic and meningeal arteries, as demonstrated by magnetic resonance angiography and high-resolution ultrasonography [37, 53–60]. While some substances, such as NO donors and K_{ATP}channel openers, dilate cerebral vessels, endogenous peptides like CGRP and PACAP-38 primarily dilate extracerebral arteries due to poor blood-brain barrier penetration, suggesting that their peripheral action is sufficient to induce migraine attacks [54, 56]. Moreover, migraine-inducing substances, such as CGRP, do not induce pain when administered subcutaneously in either cephalic or extracephalic regions [61, 62], and some possess anti-nociceptive effects when administered centrally [63]. This indicates that their migraine-inducing effects are not mediated through direct neuronal action but involve vascular mechanisms.

Vessel-to-neuron signaling mechanisms

Our hypothesis is that the migraine-inducing potential of all identified molecular triggers is related to their common effects on VSMCs within the walls of meningeal arteries (Fig. 1). In this unified cascade, neuropeptides bind to G-protein-coupled receptors on VSMCs, increasing intracellular cAMP levels [64–66]. Elevated cAMP leads to the phosphorylation and opening of specific potassium channels, including K_{ATP} channels and BK_{Ca}channels [67]. Notably, these channels can also be activated via a parallel cGMP–dependent pathway that mediates the effects of NO and soluble guanylate cyclase [68].

The culmination of these intracellular events is the efflux of potassium ions, resulting in hyperpolarization of the VSMC membrane and subsequent dilation of intracranial arteries. Pharmacological inducers, such as K_{ATP} channel openers and BK_{Ca}channel openers, act directly on these potassium channels, facilitating potassium efflux [37, 71]. Given that all migraine-inducing substances exert their effects on extracerebral arteries—particularly the meningeal arteries—but only some affect cerebral arteries, it is likely that these vascular events unfold predominantly in the extracerebral vasculature [37, 53–60].

The resulting vasodilation and associated potassium efflux are hypothesized to lead to depolarization of adjacent perivascular nociceptive afferents, initiating pain transmission along the trigeminovascular pathway. As mentioned before, this vessel-to-neuron signaling can involve two principal mechanisms. First, vasodilation

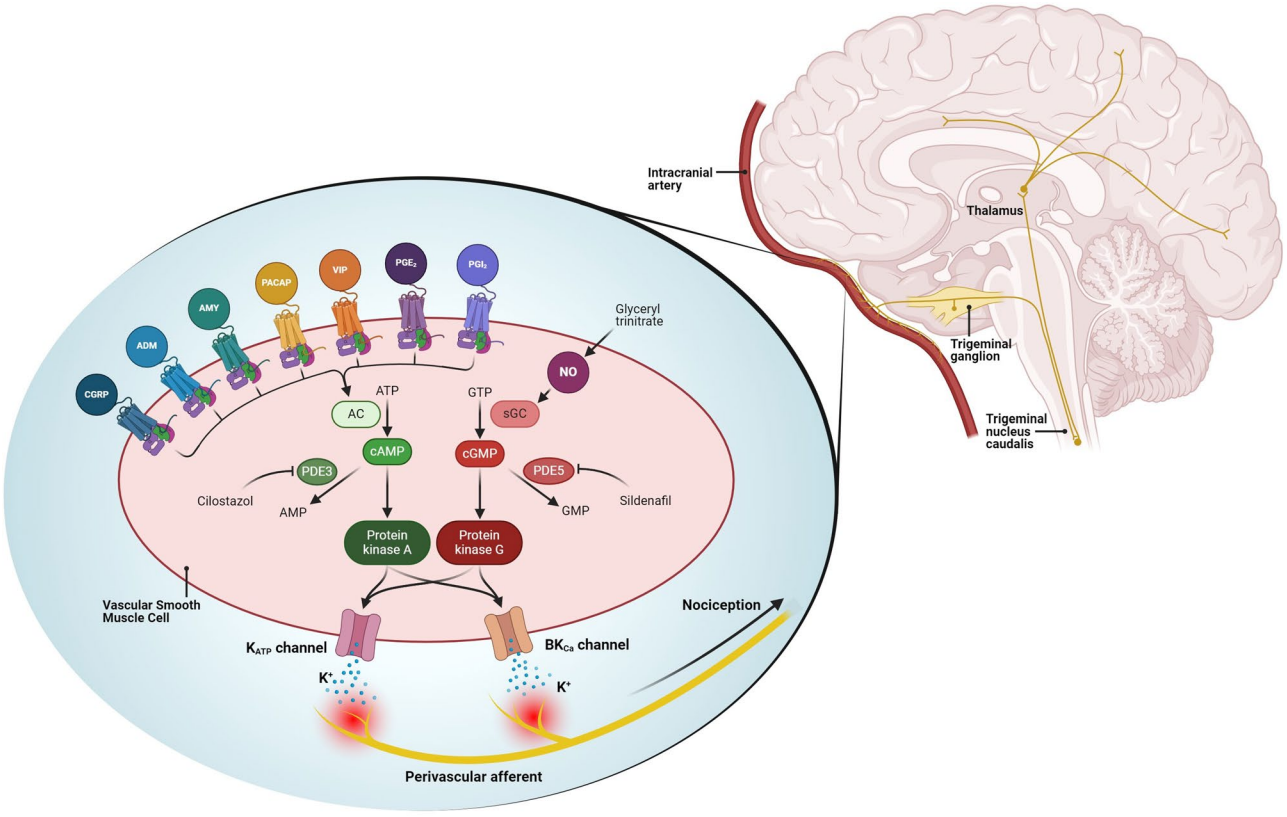

Fig. 1 Hypothesized Vessel-to-Neuron Signaling in Migraine Pathophysiology. Both endogenous and exogenous migraine-inducing agents converge on a shared signaling cascade in vascular smooth muscle cells (VSMCs) of intracranial arteries, particularly within the meninges. At the cell surface, neuropeptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP) bind to their receptors and stimulate adenylate cyclase (AC), thereby increasing intracellular levels of cyclic adenosine monophosphate (cAMP) [64–66]. Cilostazol, another potent migraine trigger, further elevates cAMP by inhibiting phosphodiesterase-3 (PDE3)–mediated degradation [69]. In a parallel pathway, glyceryl trinitrate donates nitric oxide (NO) to activate soluble guanylate cyclase (sGC), which raises cyclic guanosine monophosphate (cGMP) [68]. Sildenafil sustains this effect by blocking phosphodiesterase-5 (PDE5), preventing cGMP breakdown [70]. Elevated levels of cAMP and cGMP then activate protein kinases that phosphorylate and open potassium channels, including ATP-sensitive (K_{ATP}) and BK_{Ca}channels, leading to potassium efflux [67, 68]. This efflux is believed to depolarize perivascular trigeminal afferents, generating nociceptive signals that travel via the trigeminal ganglion to second-order neurons in the spinal trigeminal nucleus, and subsequently to third-order neurons in the thalamus. From the thalamus, nociceptive information projects to cortical regions such as the primary somatosensory cortex, insula, and visual cortex, ultimately giving rise to the perception of migraine headache [17] AC, adenylate cyclase; ADM, adrenomedullin; AMY, amylin; PDE3, phosphodiesterase-3; PDE5, phosphodiesterase-5; PGE_2, prostaglandin E_2; PGI_2, prostaglandin I_2; sGC, soluble guanylate cyclase; VIP, vasoactive intestinal peptide

causes mechanical stretching of the vessel wall, providing a mechanical stimulus that activates nearby nociceptors. Second, the efflux of potassium from VSMCs increases the extracellular potassium concentration in the perivascular space. This elevation in extracellular potassium might depolarize nearby nociceptors by shifting their resting membrane potential toward threshold, facilitating action potential generation [2]. This chemical form of vessel-to-neuron signaling is compelling, considering that direct application of potassium ions to nociceptors is a well-established method of inducing depolarization [34].

Case example calcitonin gene-related peptide signaling

A plausible example of vessel-to-neuron signaling in migraine pathogenesis involves the CGRP pathway. Intravenous infusion of CGRP reliably induces migraine attacks in people with migraine [72–74], underscoring its pathogenic role. Notably, pre-treatment with erenumab—a monoclonal antibody targeting the CGRP receptor—reduces CGRP-induced migraine attacks to 27% (10 of 37 participants), compared with 53% (20 of 38 participants) in those receiving placebo [75]. Despite this robust effect, erenumab did not prevent migraine attacks induced by cilostazol, a phosphodiesterase 3 inhibitor that elevates intracellular cAMP downstream of the CGRP receptor [75]. Erenumab also failed to prevent migraine attacks induced by sildenafil [76], which acts via the cGMP-dependent pathway, or by levcromakalim, a K_{ATP}channel opener [77]. These observations suggest that erenumab mediates its therapeutic benefits in VSMCs within the walls of intracranial arteries. Once downstream effectors

of cAMP or other parallel routes are activated, CGRP receptor blockade alone cannot prevent migraine attack initiation.

Interestingly, erenumab has shown no efficacy in trigeminal neuralgia, a disorder characterized by recurrent attacks of severe facial pain that arise from direct irritation of the trigeminal nerve [78]. In a recent randomized, double-blind, placebo-controlled trial, erenumab failed to reduce pain intensity or attack frequency in participants with trigeminal neuralgia when compared to placebo [79]. This contrast with erenumab's success in preventing migraine attacks highlights the distinct pathophysiological mechanisms underlying the two disorders. Whereas trigeminal neuralgia is thought to result from direct nerve irritation, migraine likely depends on CGRP-mediated intracranial vasodilation and subsequent perivascular meningeal nociceptor activation. Thus, the absence of benefit in trigeminal neuralgia further underscores the intracranial vasculature's importance in migraine pathogenesis. If CGRP-receptor blockade is insufficient to mitigate trigeminal pain arising from purely neural irritations, yet effectively prevents migraine attacks, it supports the notion that migraine involves a critical vessel-to-neuron signaling component in its pathogenesis.

Case example vascular K_{ATP} channel modulation

Another compelling example of vessel-to-neuron signaling in migraine arises from the role of K_{ATP} channels. Historically, opening these channels was considered analgesic, as preclinical pain models showed that K_{ATP} channel opening could hyperpolarize neurons and diminish their excitability [80–82].

However, mounting evidence has revealed the opposite outcome in migraine provocation models. K_{ATP} channel openers can potently induce migraine attacks in people with migraine [36], pointing to an alternative mechanism centered on VSMCs. K_{ATP} channel opening leads to hyperpolarization of VSMCs and thus promotes vasodilation [32]. This vasodilation, coupled with increased potassium efflux, might explain findings that opening of K_{ATP} channels activate meningeal nociceptors [35]. In support, intravenous infusion of a K_{ATP} channel opener selective for neurons alone does not induce migraine attacks in people with migraine [83]. Moreover, preclinical data has demonstrated that vascular K_{ATP} channel openers are essential for both arterial dilation and headache-like behaviors induced by K_{ATP} channel openers and NO donors [38]. These results further underscore how vessel-to-neuron signaling plays an important role in migraine pathogenesis.

Case example vasoactive intestinal polypeptide signaling

A notable aspect of migraine attack induction involves not only the magnitude of vascular changes but also their duration. One of the most compelling examples of this concept derives from vasoactive intestinal polypeptide (VIP), a peptide with potent yet short-lasting cranial vasodilatory effects [58, 84]. When a 20-minute intravenous infusion of VIP is administered to people with migraine, it produces only a brief dilation of cranial arteries and results in low migraine induction rates (0–18%) [84]. However, extending the infusion to 120 min elevates the migraine attack induction rate to an impressive 71%, coinciding with a sustained vasodilatory response [58].

This dramatic escalation underscores how prolonged vasodilation might transform what could otherwise be a subthreshold phenomenon into a full-blown migraine attack. The extended VIP infusion effectively mimics the vascular effects observed with other established molecular migraine triggers, such as CGRP and PACAP [54, 56]. The difference might, in part, be related to VIP's anti-inflammatory effects on mast cells [85], whereas PACAP-38's ability to degranulate mast cells is thought to contribute to both prolonged vasodilation and migraine induction. Such evidence further supports the broader argument that vessel-to-neuron signaling, characterized by sustained vasodilation and subsequent nociceptor activation, is central to migraine attack generation.

Case example pituitary adenylate cyclase-activating polypeptide

Although a 20-minute intravenous infusion of VIP induces only transient vasodilation, the related neuropeptide PACAP-38 produces a more sustained dilation of cranial arteries [56]. This prolonged effect may explain PACAP-38's strong migraine-inducing potential, as even a brief 20-minute infusion triggers migraine attacks in up to 58% of individuals with migraine [51]. The role of vasodilation in this process is further supported by evidence that early administration of sumatriptan—a known cranial vasoconstrictor—significantly reduces the incidence of PACAP-38–induced migraine attacks [86]. Recent findings also show that PACAP-38 activates meningeal nociceptors, possibly through indirect vascular mechanisms such as persistent dilation of meningeal arteries [87]. Notably, this nociceptor activation was blocked by dural application of lidocaine, implicating the dura mater as a key site of PACAP-38's migraine-generating action [87]. Collectively, these observations suggest that prolonged meningeal vasodilation might be a critical mediator of migraine attacks.

Lateralization of pain corresponds to vascular changes

Evidence from neuroimaging studies supports the idea that vascular events drive trigeminal nociceptor activation in migraine [88]. Some studies report that vasodilation occurs on the pain side during spontaneous migraine attacks. For example, one study using magnetic

resonance angiography demonstrated that people with unilateral headache exhibited dilation of intracerebral arteries on the pain side [88]. Another study using ultrasound found decreased blood flow velocity in the middle cerebral artery (MCA) on the headache side, suggesting lateralized vascular changes [89].

Similar observations have emerged from migraine provocation models. During CGRP-induced migraine attacks, both the middle meningeal artery (MMA) and MCA dilated ipsilaterally in people with unilateral headache, and bilaterally in those with bilateral headache [90]. Notably, CGRP alone does not dilate the MCA when given intravenously [54], implying that the observed dilation reflects processes tied to the induced migraine attack.

However, not all findings point in the same direction. In a study investigating PACAP-38–induced migraine attacks, arterial diameters did not differ between the painful and non-painful sides, and the cervical intracarotid artery even showed reduced diameter [56]. This study might have been underpowered to detect subtle lateralized changes. Another investigation of nitroglycerin-induced migraine attacks likewise found no difference in vasodilation between the painful and non-painful sides, nor an overall increase compared with placebo [91]. Despite these discrepancies, several lines of evidence suggest that cranial vasodilation often localizes to the side of migraine pain, supporting the argument that vessel-to-neuron signaling plays a causal role in migraine pathogenesis.

Therapeutic implications blocking vessel-to-neuron signaling

Triptans and ergot alkaloids—two commonly used serotonergic agents for migraine—might derive part of their therapeutic efficacy from their vasoconstrictive properties [92]. In contrast, the 5-HT_{1F} agonist lasmiditan, which lacks vasoconstrictive activity, demonstrated lower efficacy than triptans in a recent network meta-analysis and was associated with more frequent central side effects [93]. Despite this limitation, lasmiditan likely suppresses neurogenic inflammation, thereby also indirectly mitigating vessel-to-neuron signaling [94].

As mentioned above, molecular triggers induce dilation of cranial arteries in migraine provocation models. Interestingly, a study investigating PACAP-38 found that sumatriptan's vasoconstrictive effect reversed this dilation and prevented the onset of migraine attacks [86]. Likewise, sumatriptan exhibited comparable vasoconstrictive effects following CGRP administration [49].

Another clear indication of vascular involvement in migraine emerges from treatments that target vasodilatory neuropeptides. Indeed, blocking the CGRP pathway with monoclonal antibodies or gepants has proven effective for both acute and preventive migraine treatment [95–97]. Human experimental data further support this notion by showing that erenumab—a monoclonal antibody directed against the CGRP receptor—attenuates vasodilation and reduces migraine induction in people with migraine who receive intravenous CGRP infusion [75]. Moreover, a recent phase II trial has demonstrated that a monoclonal antibody targeting the PACAP ligand was superior to placebo in preventing migraine attacks [98]. Notably, this same antibody prevented dilation of the cranial arteries following PACAP-38 infusion in healthy adults [99]. By contrast, an antibody targeting the neuronal PAC_1 receptor, rather than vascular PACAP-responsive receptors, failed to prevent migraine attacks [100].

It is also important to note that both monoclonal antibodies and gepants cross the blood–brain barrier only to a minimal extent because of their size and hydrophilicity [101, 102]. Consequently, they likely exert their primary effects outside the CNS, where inhibiting vessel-to-neuron signaling might underlie their therapeutic efficacy.

Integration with cortical spreading depression and aura

In spontaneous migraine attacks, an important trigger is aura and its neural substrate, cortical spreading depression (CSD)—a wave of neuronal depolarization that gradually spreads across the cerebral cortex [103]. In the wake of this depolarization, a host of nociceptive and inflammatory mediators are released, which may, in turn, sensitize and depolarize meningeal nociceptors [104, 105]. These mediators also exert pronounced vascular effects, initiating transient constriction followed by prolonged dilation of dural arteries [103]. The interplay between chemical effects of CSD and mechano-chemical vascular signaling might provide the input for subsequent nociceptor activation and migraine headache. Interestingly, some research suggests that the relationship between CSD and nociceptor activation might be bidirectional. In a recent open-label study, CGRP was capable of inducing aura in 38% of patients with migraine with aura [106]. This implies that CGRP might act through vascular pathways to induce trigeminal activation that eventually reaches the visual cortex, providing an excitatory stimulus capable of initiating CSD.

Complementing the established trigeminovascular hypothesis

The vessel-to-neuron trigeminovascular hypothesis builds upon and complements the traditional TVS hypothesis. While the latter emphasizes neurogenic inflammation as a primary driver, the vessel-to-neuron hypothesis highlights intracranial vasodilation as an initiator of migraine attacks [2]. Recognizing intracranial

vasodilation as both a cause and effect creates a more comprehensive understanding of migraine pathogenesis.

Unified Pathophysiological Model

Trigger exposure

Various internal and external factors, such as stress, hormonal fluctuations, environmental stimuli, CSD, and vasodilatory agents, initiate vascular changes [52, 103, 107].

Vasodilation initiation

These triggers cause dilation of intracranial arteries, leading to mechanical and chemical alterations in the vascular environment [37, 53–60].

Vessel-to-Neuron signaling

Vasodilation activates trigeminal nociceptors through mechanical stretch of mechanosensitive channels and increased extracellular potassium levels.

Neurogenic inflammation

Activated nociceptors release neuropeptides (e.g., CGRP, substance P), causing further vasodilation, vascular permeability, and recruitment of immune cells [44, 47, 48].

Peripheral sensitization

Ongoing vessel-to-neuron signaling and neurogenic inflammation sensitize peripheral nociceptors, enhancing responsiveness to stimuli [22].

Central sensitization

Sustained peripheral input leads to central neuronal hyperexcitability, contributing to chronic migraine patterns [15, 108].

Migraine attack manifestation

The combined peripheral and central sensitization culminates in a migraine attack, characterized by the typical headache and associated symptoms.

Conclusions

In summary, the vessel-to-neuron trigeminovascular hypothesis integrates intracranial vasodilation and trigeminal nociceptor activation into a coherent model of migraine pathogenesis. By recognizing vasodilation as both a trigger and a downstream effect, it reconciles vascular and neuronal theories within a single framework. This approach clarifies the potency of pharmacological migraine triggers and the efficacy of peripherally acting treatments. Ultimately, targeted disruption of vessel-to-neuron signaling might offer new avenues for preventing and treating migraine attacks.

Response to Karsan & Goadsby The Journal of Headache and Pain, 2025 [109]

The question of migraine pathogenesis continues to pivot on a long-standing dichotomy: central neural origin versus meningeal (i.e., peripheral) initiation. In their critique of the vessel-to-neuron trigeminovascular hypothesis, Karsan and Goadsby advocate for a CNS-centric model of migraine initiation, assigning primacy to a plethora of non-headache symptoms. While rhetorically polished, their claims are undermined by conflicting empirical evidence, methodological weaknesses, and conceptual oversights.

They begin by drawing a linguistic distinction between *pathogenesis* (cause) and *pathophysiology* (process), as if causality were merely an abstract debate rather than a scientific question. Yet, if meningeal vasodilation—induced by well-characterized agents—initiates a cascade that reproducibly results in a migraine attack, the evidence for a causal relationship is both compelling and robust.

What follows is our point-by-point response to Karsan and Goadsby's core claims—clarifying misconceptions and reaffirming the vessel-to-neuron trigeminovascular hypothesis as the most coherent and empirically supported model of migraine pathogenesis.

Premonitory symptoms: nonspecific and inconsistent

Karsan and Goadsby build their central-origin thesis on the premise that premonitory symptoms—fatigue, mood changes, yawning, food cravings—predict imminent migraine attacks. This premise, however, collapses under empirical scrutiny.

A 2022 meta-analysis found that only 29% of individuals with migraine report any premonitory symptoms—the vast majority do not [110]. Among those who do, symptoms are highly variable and commonly observed in people with tension-type headache or no headache disorder at all [110, 111]. Fatigue affects more than 20% of the general population [112]; yawning occurs up to 20 times daily in healthy individuals [113, 114]. These are everyday phenomena, not reliable predictive markers.

Moreover, diary studies often show that patients record headache or neck pain during the supposed premonitory phase [110, 115, 116], directly contradicting the ICHD-3 definition of this period as pain-free [1]. If patients cannot reliably distinguish the prodrome from the headache phase, the use of premonitory symptoms to identify migraine attack initiation is fundamentally compromised.

Ultimately, Karsan and Goadsby's logic rests on a flawed assumption: that premonitory symptoms require a central origin. Yet symptoms such as nausea, vomiting, and photophobia are also present in disorders of clearly peripheral etiology—including meningitis and subarachnoid hemorrhage [24, 117–119]. These features are not exclusive to CNS dysfunction. Likewise, allodynia is a

normal physiological response that arises around sites of peripheral injury [120, 121].

Inferring causation from temporal correlation risks conflating coincidence with origin. CNS symptoms might reflect the brain's response to peripheral events —but they do not define the origin of the disease.

Neuroimaging of the premonitory phase: methodologically fragile, biologically ambiguous

Karsan and Goadsby rely heavily on neuroimaging studies suggesting activation in CNS structures—particularly the hypothalamus—prior to headache onset. However, many of these studies suffer from methodological limitations that undermine their conclusions.

Several involved small sample sizes (often fewer than 10 participants), liberal statistical thresholds, and post hoc region-of-interest selection [9, 10, 122–124]. One often-cited study identified activation in 26 brain regions—a pattern more plausibly attributed to statistical noise than to a biologically coherent response [9].

Even when experimentally induced by agents like nitroglycerin, premonitory symptoms often follow mild headache [9, 41, 124]. In such cases, central activation observed on imaging is more plausibly interpreted as a downstream response to peripheral nociceptor activation—not as the initiating event. Functional neuroimaging, therefore, might illustrate involvement in the migraine process, but it does not establish the site of origin. In contrast, the vessel-to-neuron hypothesis identifies a specific initiating mechanism: meningeal vasodilation followed by nociceptor activation, setting the migraine cascade in motion.

Provocation studies: meningeal vasodilation as the universal precursor

The most decisive body of evidence comes from human provocation studies. Every identified migraine-inducing peptide—adrenomedullin, amylin, CGRP, PACAP, VIP—produces meningeal vasodilation and does not cross the blood–brain barrier in meaningful quantities [51, 56, 90, 125–128]. Yet these agents consistently trigger migraine attacks in individuals with migraine, but not in healthy volunteers.

In contrast, non-vasodilatory agents such as endothelin fail to provoke migraine despite systemic effects [129]. This asymmetry is not only statistically significant—it is causally meaningful. Vasodilatory agents likely activate mechanosensitive and chemosensitive nociceptors embedded in meningeal vessels—nociceptors primed to respond to vascular stretch, ionic shifts, and neuropeptide signals. Dismissing vessel-to-neuron signaling on the basis that migraine headache lacks pulse-synchrony is akin to rejecting fire as the cause of smoke because the smoke doesn't always rise in a straight line. The absence of perfect temporal alignment does not negate causality—it reflects the inherent complexity of downstream biological responses.

To date, no pharmacologic agent has induced migraine in humans without involving meningeal vasodilation. Comparable causal evidence for a CNS-centric model remains absent.

Therapeutic evidence: peripheral blockade, durable efficacy

If migraine initiation was centrally-driven, effective treatments should require CNS penetrance. Yet most potent preventives—monoclonal antibodies against CGRP and its receptor—do not cross the BBB in meaningful amounts [130]. Their robust efficacy likely arises from inhibiting peripheral vessel-to-neuron signaling in the meninges.

Agents like gepants and lasmiditan, though non-vasoconstrictive, act on peripheral terminals to inhibit neuropeptide release and downstream inflammatory cascades [131–133]. Ubrogepant, notably, aborts attacks when administered during the presumed premonitory phase—before pain onset—despite very limited evidence of CNS penetration [134, 135].

This pharmacologic pattern strongly supports the notion that peripheral inhibition can abort migraine attacks, even those processed centrally. If migraine originated purely in the CNS, such treatments would not work. The fact that they do—reliably and across diverse patient populations—renders the CNS-centric hypothesis pharmacologically untenable.

Pathophysiological integration: peripheral initiation, central participation

Karsan and Goadsby present a false dichotomy: central *versus* peripheral. Migraine, like most pain disorders, is not defined by binaries—it is a systems-level disorder in which peripheral events trigger central cascades.

We propose that meningeal vasodilation activates perivascular afferents, triggering ascending signals to the trigeminocervical complex, hypothalamus, and cortex—where the migraine headache is processed, modulated, and ultimately perceived.

To date, no centrally acting agent, independent of peripheral mechanisms, has been shown to induce migraine attacks. In contrast, peripheral agents—including anti-CGRP antibodies and certain peptides—can consistently prevent or provoke migraine [51, 90, 130]. The evidence thus supports a model in which migraine attacks are initiated peripherally and then engage central pathways.

Conclusion: a causal model anchored in experimental data

The vessel-to-neuron trigeminovascular hypothesis is not the only model proposed to explain migraine pathogenesis—but it is, to date, the most experimentally anchored, mechanistically coherent, and clinically validated. It accounts for the ability of vasoactive agents to trigger migraine and the success of peripherally acting therapeutics that operate independently of CNS penetration.

While alternative hypotheses emphasize central initiation, none have matched the predictive or explanatory power of this model across provocation studies and therapeutic outcomes. Correlation, however suggestive, is not causation. The burden of proof lies not in theoretical appeal but in reproducible biology—and current data consistently implicate the meninges and its vasculature.

The vessel-to-neuron trigeminovascular hypothesis offers a compelling roadmap: a structured, testable framework through which future research can clarify the initiation, propagation, and modulation of migraine attacks. As with any scientific model, its value will be determined empirically—through verification, refinement, or falsification. Ultimately, progress in understanding migraine pathophysiology will be driven not by theoretical preference, but by empirical rigor.

We thank our colleagues for sharing their perspectives. Rigorous, evidence-based discourse is vital for advancing the science of headache disorders—and for improving patient care.

Abbreviations

BK_{Ca} channel	large conductance calcium-activated potassium channel
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CSD	cortical spreading depression
TVS	trigeminovascular system
K_{ATP} channel	ATP-sensitive potassium channel
MCA	middle cerebral artery
MMA	middle meningeal artery
NO	nitric oxide
PACAP	pituitary adenylate cyclase-activating polypeptide
TCC	trigeminocervical complex
VIP	vasoactive intestinal polypeptide
VSMC	vascular smooth muscle cell

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Authors' contributions

R.H.C. wrote the first draft of the manuscript. H.A., and M.A. revised the manuscript for intellectual content.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

RHC has received personal fees from Teva, Pfizer, and Lundbeck, outside of the submitted work, has received honoraria from Neurotorium, and serves as section editor for the Journal of Pain Research. HA has received personal fees from AbbVie, Lundbeck, Pfizer, and Teva, outside of the submitted work. HA also serves on the Editorial Board of The Journal of Headache and Pain. MA has received personal fees from AbbVie, AstraZeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Pfizer, and Teva, outside of the submitted work; has received funding from Danish National Research Foundation, Lundbeck Foundation, Novo Nordisk Foundation, Novartis, and Lundbeck; serves as an associate editor for The Journal of Headache and Pain and associate editor for Brain; and serves on the editorial board of Neurotorium and has received honoraria.

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