TRPV1-mediated central sensitisation: Core mechanisms of migraine chronification and novel targeted therapeutic strategies (Review)

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Abstract. Migraines are highly prevalent and disabling neurological disorders. Central sensitisation constitutes the core pathophysiological basis for its recurrent and chronic nature. Transient receptor potential vanilloid 1 (TRPV1), a key molecule in pain signalling, is not only involved in peripheral nociception, but is also highly expressed in central pain-processing regions. TRPV1 directly contributes to the initiation and maintenance of central sensitisation, positioning it as a promising therapeutic target for migraine management. The present review systematically summarised the biological characteristics of TRPV1 and its associations with central sensitisation and migraines. The molecular mechanisms through which TRPV1 mediates central sensitisation are elaborated upon, including the regulation of neurotransmitter release, activation of glial cells, involvement in inflammatory responses and modulation of synaptic plasticity. Furthermore, the research progress and clinical challenges of TRPV1-targeted strategies are discussed, including antagonists, agonists and genetic regulation. Lastly, the present study proposes future research directions at both basic and clinical levels, providing a novel molecular perspective on migraine pathogenesis and establishing a theoretical foundation for the development of targeted clinical therapies.

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Contents

1. Introduction

Migraines are a leading cause of disability among neurological disorders worldwide. They are characterized by recurrent episodes of moderate to severe throbbing headaches, often accompanied by photophobia, phonophobia and nausea. Severe cases may also result in disability (1). The global prevalence of migraine is continuing to rise (2) and although the burden remains markedly higher in women compared with men, the rate of increase is faster among male patients. Notably, prevalence among adolescents is also increasing rapidly (2,3).

The pathogenesis of a migraine remains incompletely understood. Previous research (4,5) has implicated abnormalities in neurovascular regulation, genetic factors, endocrine disorders, environmental triggers and psychophysiological factors. For example, in polycystic ovary syndrome, an imbalance in the neuropeptide regulatory network has been reported to contribute towards central-peripheral neuroendocrine dysfunction (6). However, growing evidence indicates that central sensitisation is the core pathophysiological basis for recurrent and chronic migraines (7,8). Central sensitisation

refers to a persistent, plastic increase in the reactivity of neurons in the central nervous system (CNS) pain pathways. Clinically, it manifests as a lowered pain threshold (hyperalgesia), pain responses to non-noxious stimuli (allodynia) and expansion of pain distribution, all key contributors to characteristic migraine symptoms such as hyperalgesia and touch-induced pain (9-11). Recent studies have further demonstrated that persistent inflammatory stress driven by cellular senescence can exacerbate abnormal CNS plasticity. Although this mechanism has been primarily described in neurodegenerative diseases such as Alzheimer's disease, it offers a new perspective for understanding the long-term maintenance of central sensitisation in migraines (12).

The transient receptor potential (TRP) channel family comprises non-selective cation channels widely distributed on mammalian cell surfaces. These channels have been implicated in a number of physiological processes, including temperature sensing, mechanotransduction and chemical signal transduction (13,14). TRPV1, also known as the capsaicin receptor, belongs to the TRPV subfamily and can be activated by numerous stimuli, including capsaicin, temperatures >43˚C and acidic environments (pH <5.9). TRPV1 serves a key role in pain signal transmission (15,16). In the pathophysiology of a migraine, inflammatory factors released from the meninges, such as calcitonin gene-related peptide (CGRP), nitric oxide (NO) and prostaglandins, along with local tissue acidification, markedly activate and sensitize TRPV1 on trigeminal ganglion (TG) neurons, initiating pain signal transmission to the CNS (17). Membrane functional proteins and ion channels can serve as key biomarkers for disease prognosis and targeted intervention, offering notable references for precision therapeutic screening (18).

Previous studies have reported the presence of TRPV1 expression in key CNS regions involved in nociceptive processing, including the trigeminal nucleus caudalis (TNC), thalamus and periaqueductal grey (PAG) (19,20). At the central level, TRPV1 directly participates in regulating presynaptic neurotransmitter release and postsynaptic neuronal excitability. TRPV1 also influences plasticity changes such as long-term potentiation (LTP) and promotes glial cell activation and the release of pro-inflammatory cytokines. These actions collectively drive the formation and maintenance of central sensitisation (21,22). Therefore, targeting TRPV1 may not only block initial pain afferent transmission but also directly intervene in central sensitisation, offering new preventive and therapeutic strategies for migraine management. Adjunctive measures, such as nutritional interventions and homeostatic regulation, can effectively modulate neuronal excitability and physiological status, providing complementary approaches for the comprehensive management of chronic neuropathic pain (23).

Although previous reviews have explored the role of TRPV1 in pain transmission or the mechanisms of central sensitisation in migraine, the majority of studies have focused solely on peripheral nociceptors. However, a systematic, integrated analysis of the direct involvement of TRPV1 in the development and maintenance of central sensitisation within central pain-processing regions is lacking. Therefore, the present review adopted 'TRPV1-mediated central sensitisation' as a unified theoretical framework to systematically elucidate the molecular mechanisms underlying migraines. The aim was to provide new theoretical foundations and translational insights for research into the pathogenesis of a migraine and its clinical treatment.

2. Associations between central sensitisation and migraines

Core characteristics of central sensitisation. Central sensitisation is a pathological state in which pain transmission pathways of the CNS (primarily including the spinal dorsal horn, trigeminal spinal tract nucleus, thalamus and cerebral cortex) exhibit abnormally heightened excitability following prolonged exposure to painful stimuli. First proposed and demonstrated by Woolf (24) in 1983, it is the core pathological basis for the development of chronic pain. The clinical features of central sensitisation include a lowered pain threshold, hyperalgesia, allodynia and expanded pain distribution, which closely align with the sensory abnormalities observed in migraines, such as scalp tenderness, photophobia and phonophobia (25,26).

Clinical studies have found that the pressure pain threshold in patients with migraines is markedly lower compared with that of healthy individuals. This represents the core quantitative manifestation of central sensitisation (27,28). The degree of pain sensitivity is associated with both the headache attack frequency and the extent of disease chronicity, with a more notable reduction in pain threshold observed in patients with chronic migraines (29,30). The underlying pathophysiological mechanisms involve abnormalities in multi-level pain regulation. The pressure pain threshold indirectly reflects the excitability levels of neurons in the spinal dorsal horn and trigeminal spinal tract nucleus (31,32). Progressive lowering of the pain threshold is associated with N-methyl-D-aspartate (NMDA) receptor-mediated LTP at spinal synapses, as well as weakened function of descending inhibitory pathways in the brainstem (32,33). Standardized reference indices established through quantitative sensory testing, including thermal and mechanical detection thresholds, thermal and mechanical pain thresholds, pressure pain thresholds and pain superposition, can objectively identify pain sensitivity phenotypes in patients with migraines. This provides a reliable basis for clinical differentiation between episodic and chronic migraine and for assessment of central sensitisation (28,34). This also indicates that central sensitisation in migraines is a continuous, dynamic process that progresses from acute to chronic, rather than a series of discrete, stage-based events.

Role of central sensitisation in migraine pathogenesis

Amplification of pain perception. During a migraine attack, the abnormal enhancement of pain perception is a multistage pathophysiological process initiated peripherally and regulated centrally (35). This process begins with the activation of the trigeminal vascular system. Its sensory nerve endings release neuropeptides such as CGRP and substance P (SP), triggering neurogenic inflammation that continuously stimulates peripheral nociceptors (36). The resulting signals are transmitted to the trigeminocervical complex (TCC) in the brainstem (37). There, through sustained activation of the NMDA receptor system, the depolarization threshold of neurons is lowered, making them prone to firing in response to normal or subthreshold stimuli. This leads to enhanced

responses and an expanded receptive field, establishing central sensitisation (38).

In addition to local sensitisation, an imbalance in the descending modulatory system connecting the PAG to the rostral ventromedial medulla (RVM) also contributes to central sensitisation. Under physiological conditions, activation of RVM 'OFF cells' projects to the TCC, releasing inhibitory neurotransmitters such as serotonin and norepinephrine to produce analgesia (39-41). However, during recurrent migraine attacks, this balance is disrupted. On the one hand, functional exhaustion of OFF cells or downregulation of inhibitory receptor sensitivity in the TCC leads to weakened descending inhibition (42,43); on the other hand, sensitized TCC abnormally drives excessive activation of RVM 'ON cells', which release excitatory neurotransmitters such as glutamate to the TCC, enhancing its excitability (44,45). The combined effects of weakened descending inhibition and enhanced facilitation amplify pain signals at the central level.

Chronicity and recurrence. Central sensitisation is the core pathological mechanism underlying the transition from an episodic to chronic migraine. Acute attacks originate from activation of the peripheral trigeminal neurovascular system and CGRP release, with nociceptive signals continuously ascending to the TNC (46,47). If attacks recur, this leads to enhanced glutamatergic transmission, excessive NMDA/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation and an influx of Ca^{2+}. These changes induce synaptic plastic alterations such as LTP, leading to weakened endogenous inhibition and a lowered central response threshold. Ultimately, this clinically progresses to a chronic migraine, defined as ≥15 headache days per month (48,49). During this process, LTP-like synaptic potentiation occurs in pain network nodes, including the trigeminocerebellar complex, thalamus, anterior cingulate cortex and insula. Abnormal spontaneous discharges further persist between attacks, forming a cycle in which 'attacks exacerbate sensitisation and sensitisation triggers attacks (50).

Development of associated symptoms. There are a number of symptoms that accompany migraines, such as photophobia, phonophobia, nausea, vomiting and cognitive impairment. These may arise from the spread of central sensitisation from nociceptive pathways to adjacent sensory information processing pathways.

Photophobia and phonophobia originate from brainstem-thalamic sensory integration dysfunction. Abnormally excited, hypersensitive TCC ascending pathways cause the thalamus to lose its sensory filtering capacity. Physiological light and sound signals are amplified and cause abnormal activation of emotion-associated brain regions such as the insula and cingulate gyrus (51-53). In addition, blue light hypersensitivity, mediated by intrinsically photosensitive retinal ganglion cells, lowers cortical spreading depression thresholds, activating the thalamic-trigeminovascular pathway, synergistically driving photophobia with central sensitisation (54).

Nausea and vomiting arise from abnormal activation within brainstem viscerovagal-autonomic integration nuclei. The sensitized TNC enhances functional connectivity with the nucleus tractus solitarius and reticular formation through trigeminal-vagal reflexes, lowering the vomiting centre threshold (55-57). Concurrent autonomic dysfunction and vestibular-cross sensitisation abnormally couple headache signals with the vomiting reflex, causing them to occur synchronously (58,59). Furthermore, cognitive and emotional disturbances result from sensitisation spreading to the prefrontal cortex and limbic system, manifesting as fatigue, cognitive fog and mood swings. This indicates that central sensitisation has expanded to functional networks throughout the entire brain (60,61).

Role of TRPV1 in central sensitisation. Central sensitisation serves a key role in migraine pathogenesis, as numerous brain regions and signalling pathways are involved. Among these, TRPV1 is a key molecule regulating this process. Persistent injury or inflammation can upregulate the activity and expression of central TRPV1. This subsequently enhances the transmission of central pain signals, lowers the pain threshold and disrupts the excitatory-inhibitory balance, thereby amplifying and spreading pain signals (62,63). In chronic pain, sustained central TRPV1 activation may even induce structural remodelling of neural circuits. This drives central sensitisation from an acute adaptive state, to a self-sustaining pathological state (64,65).

3. Biological properties of TRPV1

TRPV1 channels are homotetramers or heterotetramers composed of four subunits. Each subunit contains six transmembrane domains (S1-S6), with both N- and C-termini located intracellularly. The pore region between S5 and S6 mediates ion selectivity (66). Functionally, the intracellular N-terminal ankyrin repeat domain participates in channel assembly and sensitisation (for example, ATP binding enhances responsiveness). Meanwhile, key residues in the C-terminal TRP domain (such as I696 and W697) serve as core sites for activation by stimuli (such as capsaicin and heat). Mutations at these sites markedly reduce sensitivity (67).

With regard to tissue distribution, TRPV1 is primarily concentrated in neural tissues involved in pain transmission, with smaller amounts present in non-neural tissues such as the cardiovascular system and skin. In the peripheral nervous system, TRPV1 is highly expressed in afferent pain fibres, such as those in the dorsal root ganglia (DRG) and TG, where it receives and transmits pain signals. In the CNS, it is widely distributed at key nodes of pain pathways, including the spinal dorsal horn, brainstem, thalamus and sensory cortical areas (68). Among these, the TG serves as the origin of afferent pain signals from the head and face, while the spinal dorsal horn acts as the core site for signal integration and regulation of central sensitisation; collectively, these structures are key targets for TRPV1 involvement in migraine pathogenesis (69). Given its specific distribution and regulatory functions in both peripheral and central pain pathways, TRPV1 serves a notable role in the central sensitisation mechanisms of migraine (70,71).

4. Mechanisms of action regarding TRPV1-mediated central sensitisation in migraines

As a key regulator of central sensitisation, TRPV1 mediates the onset and reversal of central sensitisation through a

number of synergistic mechanisms, including regulation of neurotransmitter release, activation of glial cells, the driving of inflammatory responses and modulation of synaptic plasticity.

Regulation of neurotransmitter release and disruption pain transmission homeostasis. Neurotransmitter imbalance is a key factor in the development of central sensitisation. TRPV1 alters the excitatory-inhibitory balance in pain transmission pathways by bidirectionally regulating the release of excitatory neurotransmitters (including CGRP, SP and glutamate) and inhibitory neurotransmitters [such as γ-aminobutyric acid (GABA)].

As a central neurotransmitter in migraine pathogenesis, CGRP release is tightly regulated by TRPV1. During a migraine attack, TRPV1 activation triggers an influx of Ca^{2+}. This results in two effects: It triggers the rapid release of CGRP vesicles and activates the $Ca^{2+/}$calmodulin-dependent protein kinase (CaMK)/cAMP response element-binding pathway, upregulating CGRP expression (72,73). Released CGRP binds to its receptor, activates protein kinase C (PKC) and feedback-enhances TRPV1 sensitivity, forming a positive feedback loop (74). In addition, CGRP can directly act on type 2 neurons in the trigeminal nerve, inducing the expression of the cellular proto-oncogene Fos and increasing neuronal excitability. It also promotes the polarization of microglia toward the M1 phenotype, leading to the release of inflammatory factors such as IL-1β, IL-6 and TNF-α (75,76). TRPV1 antagonists can notably inhibit CGRP release, thereby blocking this positive feedback loop (77). Furthermore, insulin can promote CGRP release by activating TRPV1, thereby increasing headache susceptibility. This further determines the key regulatory role of TRPV1 in CGRP release (73).

SP release is also regulated by TRPV1, as upon activation of TRPV1, SP is released, which in turn activates the neurokinin-1 receptor, enhancing TRPV1 activity and lowering the channel activation threshold (78,79). SP can also activate glial cells to release inflammatory factors, including TNF-α, IL-1β and IL-6, indirectly promoting central sensitisation (80-82). TRPV1 antagonists inhibit SP release, thereby blocking the initiation of peripheral inflammation and central sensitisation (83,84).

Excessive glutamate release is a direct driver of central sensitisation. TRPV1 activation promotes increased glutamate release in the spinal dorsal horn, TNC and other regions. This glutamate activates postsynaptic AMPA/NMDA/metabotropic glutamate receptors, inducing the formation of LTP. In turn, sensitized TRPV1 further promotes glutamate release, forming a cycle (48,85,86). However, TRPV1 antagonists can reduce postsynaptic neuronal excitability by blocking excessive glutamate release (87,88).

In comparison with the increase in excitatory neurotransmitters, attenuation of GABAergic inhibition represents another key mechanism of central sensitisation. First, TRPV1 activation directly reduces GABA release from inhibitory interneurons. Second, TRPV1 activation can activate kinases such as PKC and protein kinase A (PKA), leading to phosphorylation of GABA-A receptors and downregulation of their membrane expression (89). Furthermore, activated glial cells release TNF-α, inhibit glutamate decarboxylase and promote the reuptake of GABA transporters. This results in the sustained reduction of GABA in the synaptic cleft (90). Notably, GABA itself can inhibit the cAMP/PKA pathway by activating GABA-A receptors and signalling through the inhibitory G protein subtypes Gi/o, thereby causing the dephosphorylation of TRPV1. This constitutes an endogenous negative feedback mechanism (91,92). Following TRPV1 desensitisation or antagonism, GABAergic inhibition is restored (93).

The combined effect of increased release of excitatory neurotransmitters (including CGRP, SP and glutamate) and reduced activity of the inhibitory neurotransmitter (such as GABA) results in a net enhancement of synaptic transmission. This provides the necessary depolarizing basis for the establishment of LTP (Fig. 1A).

Activating glial cells to amplify the central sensitisation effect. Glial cell activation is a key step in the onset and progression of central sensitisation and TRPV1 is implicated through both direct and indirect mechanisms.

Microglial activation is an early event in initiating central sensitisation. On the one hand, microglia functionally express TRPV1 on their surface. During a migraine attack, pain signals can directly activate this channel, triggering a Ca^{2+} influx and activating the microglia. Subsequently, the NF-κB signalling pathway is activated; NF-κB enters the cell nucleus and initiates the transcription of certain pro-inflammatory factors. This upregulates the expression of effector molecules such as IL-1β, IL-6, TNF-α, NO and ROS, thereby amplifying the inflammatory response (94). Concurrently, the toll-like receptor 4 signalling pathway independently participates in neuroinflammation through its adaptor protein (myeloid differentiation primary response 88), which similarly activates NF-κB (95,96). On the other hand, upon TRPV1 activation, neurons release signalling molecules including SP and CGRP. These molecules bind to corresponding receptors on the surface of microglia through paracrine mechanisms, indirectly promoting microglial activation (97,98). Furthermore, TRPV1 antagonism effectively inhibits microglial activation and reduces the release of inflammatory cytokines (99).

Abnormal activation of astrocytes primarily contributes to the maintenance of central sensitisation. Astrocytes express small amounts of TRPV1 on their surface. Upon activation of this channel, Ca^{2+} influx triggers signalling pathways such as NF-κB and MAPK, leading to the release of inflammatory factors (IL-6 and complement C3) and neuroactive substances (ATP, glutamate and GABA). Notably, activated astrocytes exhibit downregulation of glutamate-aspartate transporter and glutamate transporter-1. This leads to a reduced capacity to clear glutamate from the synaptic cleft, resulting in glutamate accumulation. Accumulated glutamate continuously activates postsynaptic AMPA/NMDA receptors, thereby stabilizing and prolonging the hyper-excitable state of neurons (100,101). Interventions targeting TRPV1 can inhibit astrocyte activation, restore glutamate clearance capacity and reverse central sensitisation (101).

Thus, microglia serve a central role in initiating and acutely amplifying sensitisation, while astrocytes are responsible for maintaining sensitisation and facilitating its transition to a chronic state. TRPV1 further serves an important regulatory role in this continuous process (Fig. 1B).

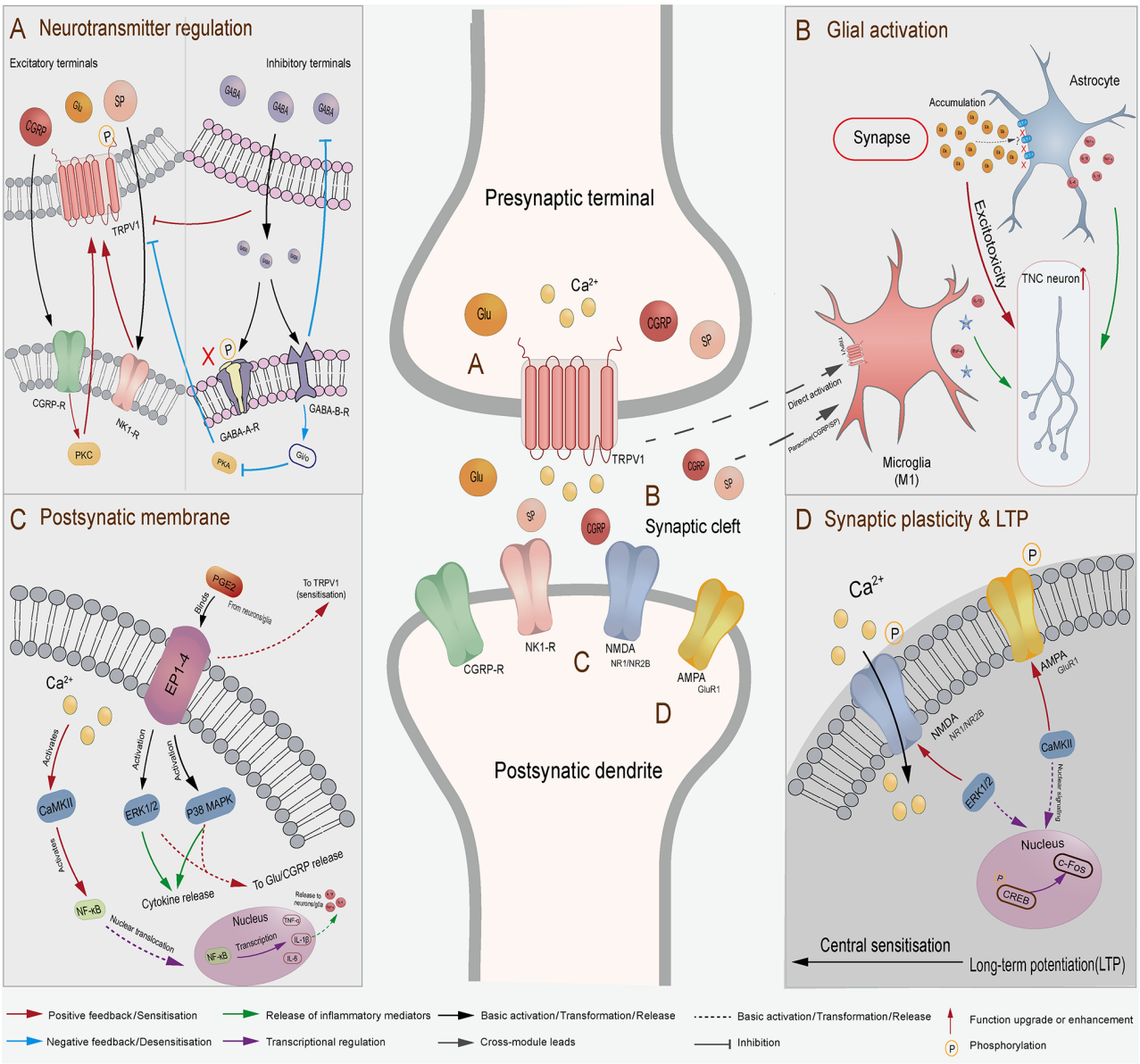

Figure 1. Schematic diagram illustrating the mechanism by which TRPV1 mediates central sensitisation in the trigeminal-cervical complex. (A) Presynaptic regulation: Positive feedback (red arrows) and negative feedback (blue arrows) loops involving excitatory (CGRP/SP/Glu) and inhibitory (GABA) neurotransmitter signals. (B) Glial cell activation: M1-type microglia release inflammatory mediators; dysfunction of reactive astrocytes' GLT-1 (red cross). (C) Inflammatory signalling pathways: PGE2 activates EP receptors, promoting cytokine transcription through CaMKII/NF-κB (purple arrows) and MAPK (green arrows) pathways. (D) Postsynaptic plasticity: CaMKII and ERK phosphorylate AMPA and NMDA receptors, respectively, driving LTP (grey area) and central sensitisation. This diagram illustrates how TRPV1 synergistically mediates central sensitisation through numerous pathways involving presynaptic, glial, inflammatory and postsynaptic mechanisms. Arrows of different colours represent specific signal transduction modes. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CGRP, calcitonin gene-related peptide; CGRP-R, CGRP-receptor; EP, prostaglandin E receptor; EP3, prostaglandin E receptor subtype 3; GABA, γ-aminobutyric acid; GLT-1, glutamate transporter 1; Glu, glutamate; GluR1, glutamate receptor 1; LTP, long-term potentiation; NK1-R, neurokinin 1 receptor; NMDA, N-methyl-D-aspartate receptor; NR1, NMDA receptor subunit 1; NR2B, NMDA receptor subunit 2B; PGE2, prostaglandin E2; PKA, protein kinase A; PKC, protein kinase C; SP, substance P; TNC, dorsal subnucleus of the trigeminal-cervical complex; TRPV1, transient receptor potential vanilloid subtype 1.

Participation in the inflammatory response and promotion the initiation of central sensitisation. TRPV1 participates in the initiation and amplification of central inflammatory responses by regulating the release of inflammatory mediators and the activation of inflammatory signalling pathways.

During a migraine attack, TRPV1 activation promotes the release of prostaglandin E2 (PGE2) from neurons and glial cells. Upon binding to its receptors (EP1-EP4), PGE2 produces two effects. First, it phosphorylates TRPV1, thereby enhancing its sensitivity. Second, it promotes the release of glutamate and CGRP. These effects collectively form a positive feedback loop that drives central sensitisation (102). TRPV1 antagonists can inhibit PGE2 release and thus block this loop (103).

Furthermore, TRPV1 activation triggers a Ca^{2+} influx. This further activates two signalling pathways. The first is the CaMKII/NF-κB pathway, which promotes the transcription and release of inflammatory cytokines such as IL-1β, IL-6 and TNF-α (104). The second involves signalling cascades such as ERK1/2 and p38 MAPK, which promotes the release of inflammatory cytokines (including TNF-α, IL-1β and

IL-6) and excitatory neurotransmitters (including glutamate, substance P and CGRP), thereby increasing neuronal excitability. Collectively, these two pathways drive central sensitisation (105,106). TRPV1 antagonists can thus inhibit the activation of the NF-κB pathway and reduce the expression of inflammatory factors. Combining them with MAPK pathway inhibitors can synergistically enhance the reversal of central sensitisation (107) (Fig. 1C).

Regulating synaptic plasticity to reshape pain transmission pathways. Changes in synaptic plasticity (particularly the formation of LTP) constitute the structural basis of central sensitisation. TRPV1 regulates synaptic plasticity through both presynaptic and postsynaptic mechanisms. Specifically, TRPV1 activation first drives the release of glutamate from presynaptic terminals. This process subsequently triggers the phosphorylation of postsynaptic NMDA/AMPA receptors and the maintenance of LTP. This sequence constitutes a temporal causal chain initiating central sensitisation (108-110).

At the presynaptic level, TRPV1 drives LTP establishment by regulating neurotransmitter release. As aforementioned, TRPV1 activation promotes the release of excitatory neurotransmitters such as CGRP, SP and glutamate. These neurotransmitters act upon corresponding receptors on the postsynaptic membrane, inducing Ca^{2+} influx and downstream signalling activation, thereby enhancing postsynaptic neuron excitability. Simultaneously, retrograde messengers released from the postsynaptic site provide feedback to the presynaptic site, further promoting neurotransmitter release. This positive feedback loop provides the necessary depolarization intensity and calcium signal accumulation for LTP formation.

At the postsynaptic level, TRPV1 contributes to LTP maintenance by regulating receptor function. The Ca^{2+} influx triggered by TRPV1 activation activates the ERK1/2 pathway, promoting phosphorylation of NMDA receptor NR1/NR2B subunits and enhancing receptor channel activity (111). Second, through a CaMKII-dependent pathway, it induces phosphorylation of the glutamate receptor 1 subunit at Ser831, thereby upregulating receptor single-channel conductance and membrane surface expression (112-114). Enhanced NMDA receptor function provides a sustained calcium signal source for synaptic plasticity, while upregulated AMPA receptor function directly increases synaptic transmission efficiency. Collectively, these mechanisms maintain the long-lasting stability of LTP. Therefore, TRPV1 antagonists can inhibit ERK1/2 activation, reduce the phosphorylation levels of NMDA/AMPA receptors, prevent LTP maintenance and reverse central sensitisation (115-117).

In summary, TRPV1 drives the establishment of LTP by regulating neurotransmitter release presynaptically; simultaneously, it maintains LTP by regulating receptor function postsynaptically. These two processes are temporally sequential and spatially coordinated, together constituting the complete mechanism by which TRPV1 regulates synaptic plasticity (Fig. 1D).

5. Recent advances in TRPV1-targeted migraine treatments

Given the role of TRPV1 in central sensitisation, interventions targeting this channel have become a new focus in migraine treatment research. The present section will go on to summarize clinical and animal studies regarding TRPV1 antagonists, TRPV1 agonists and gene regulation strategies for migraine treatment. Both PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com/) databases were searched for literature published up to December 2025. Studies were included if they met the following criteria: i) Mechanistic and preclinical studies investigating the involvement of TRPV1 in pain through central sensitisation; ii) studies involving the trigeminal nerve or central pain pathways in migraine models or other chronic pain models; and iii) studies that included measures of TRPV1 regulation and central sensitisation. Studies focusing solely on peripheral non-neural tissues or lacking any indicators of central sensitisation were excluded.

TRPV1 antagonists. TRPV1 antagonists alleviate migraine by blocking channel activity and inhibiting central sensitisation. Research regarding this strategy has spanned natural products, synthetic small molecules and peptide derivatives.

In reference to natural sources and dual-target mechanisms, petasin and isopetasin from *Tussilago farfara* root extract may simultaneously inhibit TRPV1 and transient receptor potential anchor ankyrin 1. These compounds reduce neuropeptide release from trigeminal nerve terminals, thereby blocking the transmission of peripheral signals to the CNS (118). Similarly, the natural compound PINO reverses sensory neuron sensitisation by inhibiting the NF-κB/MAPK signalling pathway. This provides a promising direction for the application of novel TRPV1 antagonists (83).

Studies on specific antagonists have provided evidence for the inhibitory effects of capsazepine. Rosta *et al* (73) and Citak *et al* (77) separately determined that capsazepine may block TRPV1 activation induced by insulin or agonists. Its effects include inhibiting neurogenic inflammation and disrupting sensitized transmission in the trigeminal pathway. Studies on Johnson & Johnson series compounds found that JNJ-38893777 and JNJ-17203212 suppress excessive sensory neuron excitation and downstream neurovascular responses (119). At the molecular level, Fan *et al* (120) showed that SAF312, through synergistic action with cholesterol, stabilizes the closed conformation of the TRPV1 channel, thereby inhibiting its activation. Furthermore, peptide-based strategies have progressed; for example, the glucagon-like peptide-1 derivative exendin 20-29 selectively blocks capsaicin-induced TRPV1 activation without causing fever-associated side effects (121). In synthetic chemistry, 2-halophenylacetamide derivatives have exhibited notable TRPV1 antagonistic activity (122).

However, clinical translation faces challenges. Despite the aforementioned studies having demonstrated the marked potential of TRPV1 antagonists in terms of source diversity and molecular mechanisms, and some compounds, such as the novel TRPV1 modulator AMG8562, have been shown to circumvent the traditional side effect of hyperthermia in preclinical studies (123), translating laboratory discoveries into clinical applications for migraines remains difficult. The analgesic effects observed in preclinical animal models are difficult to replicate in migraine patients and the risk of target-associated increases in core body temperature

persists (124,125). Despite basic research have demonstrating that TRPV1 inhibition reduces trigeminal pathway sensitisation, bridging the translational gap to develop safe and migraine-specific drugs remains a persistent challenge.

TRPV1 agonists. Unlike antagonists, agonists induce receptor desensitisation by continuously activating channels, keeping them in a prolonged inactivated state and thereby inhibiting central sensitisation. This strategy avoids side effects associated with long-term antagonist use, such as hyperthermia (126). Consequently, it offers unique advantages in the context of migraine prophylaxis.

As an established TRPV1 agonist, capsaicin has been extensively studied for its multi-target desensitisation mechanisms. A previous study demonstrated (127) that capsaicin induced degranulation of meningeal mast cells and a neuro-mediated inflammatory response by activating TRPV1. Topiramate, however, notably inhibited this process. Deng *et al* (128) further revealed that after capsaicin activated TRPV1 in DRG neurons, it upregulated sodium-potassium-chloride cotransporter 1 expression through the PKC and phosphorylated ERK pathway, leading to an increase in intracellular chloride concentration. This sensitizing effect can be reversed by subsequent channel desensitisation under sustained agonist stimulation. Furthermore, capsaicin can inhibit the voltage-gated calcium channel type 3 T-type calcium channel by almost two-fold, an effect independent of desensitisation mechanisms (129). In a comparative study, Krivoshein *et al* (130) used capsaicin as a positive control and demonstrated that the endocannabinoid arachidonoyl ethanolamine can potently inhibit TRPV1-mediated firing in the long term, although a transient excitatory effect was observed during the initial phase of administration.

Clinical translation of capsaicin remains unsatisfactory. First, the intense initial burning sensation associated with high-concentration topical capsaicin formulations is a reported adverse reaction (131). Second, even if patients tolerate treatment, continuous administration is required for numerous weeks; after discontinuation, nerve fibres regenerate, leading to pain recurrence (132), necessitating long-term or even lifelong medication, making compliance the primary challenge.

Other agonists and desensitisation strategies continue to expand molecular diversity in this field. The potent agonist resiniferatoxin (RTX) upregulates expression of pain-sensitisation molecules such as TRPV1, brain-derived neurotrophic factor and voltage-gated sodium channel subtypes 1.3 and 1.7 by activating the p38 MAPK pathway in DRGs (133). However, initial RTX administration is associated with marked local irritation, manifested as acute burning pain and inflammatory reactions. This has somewhat impacted the early clinical experience. Despite this, owing to its unique targeted pharmacological advantages, RTX still holds value in clinical translation research (134,135). Alsalem *et al* (136) determined that the non-irritant agonists arvanil and olvanil induce TRPV1 desensitisation. Notably, arvanil-induced desensitisation can be reversed by bradykinin through the EP4 pathway, resulting in resensitisation. In addition, the dietary compound 8-gingerol induces TRPV1 internalization or degradation through a 'first activation, then desensitisation' mechanism. Its analgesic effect is entirely dependent on this channel (137). Furthermore, with regard to novel agonists, one research team developed a new partial agonist, namely 4-(5-chloropyridin-2-yl)-N-(1H-indazol-6-yl) piperazine-1-carboxamide (known as CPIPC). This compound targets the Arg557 residue and is capable of concentration-dependently activating the channel and inducing desensitisation. Oral administration of this agonist alleviates inflammatory pain and effectively blocks peripheral-to-central sensitisation transmission (138).

Other therapeutic strategies targeting TRPV1. Gene regulation strategies involve epigenetic interventions or modifications of cis-acting elements to modulate TRPV1 expression in the central and peripheral nervous systems at the transcriptional level. Ghosh *et al* (139) demonstrated that the histone methyltransferase G9a in DRGs bidirectionally regulates TRPV1 expression; inhibition of G9a reverses inflammation-driven TRPV1 upregulation and pain hypersensitivity. An additional study regarding orofacial inflammation found that this pathological state downregulates DNA methyltransferase 1/3a expression in the TG. This leads to hypomethylation of the TRPV1 promoter, thereby activating its expression and driving central sensitisation (140). Lai *et al* (141) demonstrated that following nerve injury, T-box transcription factor 5 (Tbx5) accumulates and recruits GATA-binding protein 4 and bromo domain protein 4 (Brd4). These factors bind to the TRPV1 promoter, enriching histone H3 lysine 9 acetylation, thereby activating TRPV1 expression. This Tbx5/Brd4 axis provides a key reference for the mechanism underlying TRPV1 upregulation in the TNC region of a migraine. Furthermore, Price *et al* (142) reported that the human SINE-VNTR-Alu retrotransposon serves as a functional cis-regulatory element for TRPV1. Knockout of this element markedly downregulated TRPV1 expression, providing a potential target for species-specific interventions based on gene editing.

RNA interference technology can further specifically inhibit TRPV1 mRNA expression through small interfering RNA or microRNA (miRNA). In a nitroglycerin-induced chronic migraine model, researchers found that miR-155-5p expression was upregulated in the TNC region. This molecule triggered inflammatory responses and central sensitisation through targeted inhibition of silenced information regulator 1 (SIRT1). The use of miR-155-5p antagonists or SIRT1 activators can reverse this process (143). Furthermore, Li *et al* (144) demonstrated that miR-199 directly targeted TRPV1 and downregulated its expression. An additional study by Li *et al* (145) found that activation of NF-κB subunit 1 signalling pathway downregulated the expression of miR-375 and miR-455. This promoted an inhibitory effect on the 3' untranslated region of TRPV1 mRNA, leading to TRPV1 upregulation.

In summary, TRPV1 antagonists can effectively block central sensitisation but have shown poor efficacy in clinical translation and may cause hyperthermia. Agonists achieve prophylactic treatment by inducing channel desensitisation, thereby avoiding the aforementioned issues associated with antagonists. However, agonists often cause severe burning pain and inflammatory reactions in the initial stages and symptoms are prone to recurrence after discontinuation. Gene regulation and RNA interference strategies can modulate TRPV1 expression at the transcriptional level and have shown promise in

Table I. Summary of TRPV1-targeting migraine treatments and interventions.

Name of drug/intervention		Type	Mechanism of action	(Refs.)
TRPV1 antagonist	Capsazepine	Synthetic small molecules	Blocks TRPV1 activation, inhibits CGRP release and suppresses neurogenic inflammation	(73,77)
	PINO	Natural compounds	Inhibits the NF-κB/MAPK pathway and reverses receptor sensitisation	(83)
	Petasin/isopetasin	Natural product (*Tussilago farfara* root extract)	Dually inhibits TRPV1/TRPA1, reducing CGRP release	(118)
	JNJ-38893777	Synthetic small molecules	Reduces c-Fos expression and CGRP release in the brainstem	(119)
	JNJ-17203212	Synthetic small molecules	Reduces c-Fos expression and CGRP release in the brainstem	(119)
	SAF312	Synthetic small molecules	Works collectively with cholesterol to stabilize the channel in its closed conformation	(120)
	Exendin 20-29	GLP-1 analogues	Selectively blocks capsaicin activation without causing side effects on body temperature	(121)
	2-Halophenylacetamide derivatives	Synthetic small molecules	Exhibits potent TRPV1 antagonistic activity	(122)
TRPV1 agonist	Capsaicin	Natural products	Induces desensitisation upon activation of TRPV1; dually inhibits Cav3 T-type calcium channels; upregulates NKCC1 through the PKC/p-ERK pathway	(127-130)
	RTX	Potent agonist	Activates the p38 MAPK pathway in DRGs and upregulates pain sensitisation molecules such as TRPV1, BDNF and Nav1.3/1.7	(133)
	Arvanil	Non-irritant agonists	Induces TRPV1 desensitisation, which can be reversed by bradykinin	(136)
	Olvanil	Non-irritant agonists	Induces TRPV1 desensitisation	(136)
	8-Gingerol	Dietary natural product	Activates first and then desensitises, inducing TRPV1 internalisation/ degradation	(137)
	CPIPC	Novel partial agonist	Targets the Arg557 residue, concentration-dependently activates the receptor and induces desensitisation	(138)
Gene regulation	G9a inhibitor	Epigenetic Intervention	Inhibits the histone methyltransferase G9a, reversing inflammation-driven TRPV1 upregulation and pain hypersensitivity	(139)
	DNMT1/3a intervention	Epigenetic intervention	Restores methylation of the TRPV1 promoter, thereby suppressing its expression	(140)
	Interference with the Tbx5/Brd4 axis	Transcriptional regulation	Inhibits Tbx5 recruitment of GATA4 and Brd4, reducing H3K9Ac enrichment at the TRPV1 promoter	(141)
	SVA type D retrotransposon knockout	Gene Editing	Knocks out cis-regulatory elements to downregulate TRPV1 expression	(142)

Table I. Continued.

Name of drug/intervention		Type	Mechanism of action	(Refs.)
RNA interference	miR-155-5p antagonist	miRNA intervention	Inhibits SIRT1, reversing inflammatory responses and central sensitisation	(143)
	miR-199	miRNA intervention	Directly targets TRPV1 mRNA and downregulates its expression	(144)
	miR-375/miR-455	miRNA intervention	Targets the 3'-UTR of TRPV1 mRNA and reverses NF-κB1-mediated de-repression	(145)

TRPV1, transient receptor potential vanilloid 1; TRPA1, transient receptor potential ankyrin 1; CGRP, calcitonin gene-related peptide; c-Fos, cellular proto-oncogene Fos; GLP-1, glucagon-like peptide-1; Cav3, voltage-gated calcium channel 3; PKC, protein kinase C; p-ERK, phosphorylated ERK; NKCC1, sodium-potassium-chloride cotransporter 1; RTX, resiniferatoxin; DRG, dorsal root ganglion; BDNF, brain-derived neurotrophic factor; Nav, voltage-gated sodium channel; DNMT, DNA methyltransferase; Tbx5, T-box transcription factor 5; Brd4, bromodomain-containing protein 4; SVA, SINE-VNTR-Alu retrotransposon; miRNA/miR, micro RNA; mRNA, messenger RNA; SIRT1, silent information regulator 1; 3'-UTR, 3' untranslated region; NF-κB1, NF-κ subunit 1; GATA4, GATA binding protein 4; PINO, pinocembrin-7-O-3-O-galloyl-4,6-hexahydroxydiphenoyl-β-D-glucoside; JNJ, Johnson & Johnson; CPIPC, 4-(5-chloropyridin-2-yl)-N-(1H-indazol-6-yl) piperazine-1-carboxamide.

chronic migraine models. However, the majority are currently in the preclinical stage, with delivery efficiency, off-target risks and long-term safety remaining notable obstacles. Overall, each strategy exhibits both advantages and limitations. Future research should therefore seek to make breakthroughs in targeting precision, delivery methods and safety assessment (Table I).

6. Conclusions

Within the present review, the key mechanisms underlying the chronicisation of migraines were systematically elucidated. The present review focused on TRPV1-mediated central sensitisation thus provided a basis for clinically stratified interventions. By analysing the advantages and disadvantages of antagonists, agonists and gene regulation, the present identified translational bottlenecks (such as the side effect of hyperthermia) and strategies to circumvent them. This may therefore direct targeted drug development and harbour clear clinical value. Despite this, a number of key issues remain to be addressed in current research.

Limitations of existing research. Although current studies regarding the role of TRPV1-mediated central sensitisation in migraine pathogenesis have established its central regulatory function, numerous key questions remain. First, the precise regulatory mechanisms of TRPV1 have yet to be thoroughly elucidated at the molecular level, for example, the specific phosphorylation sites of TRPV1 by different kinases (PKC, PKA and CaMKII) and their functional differences remain incompletely understood (146,147). Furthermore, the activation patterns and downstream signalling differences of the channel across numerous cell types (including neurons, microglia and astrocytes) require further investigation (97,147). These gaps limit the ability to precisely intervene in TRPV1 function. Second, there is a marked translational gap between existing animal models and clinical migraines. The majority of studies utilize models of inflammatory pain or nerve injury and there is a lack of ideal models capable of simulating the spontaneous onset and chronic progression of migraines. Furthermore, the pathological characteristics of the widely used nitroglycerin-induced model have yet to be validated for their correspondence with clinical migraines (148-151).

Building upon this, the clinical translation of TRPV1-targeted drugs also faces unique challenges. TRPV1 antagonists exert their effects by blocking pain signal transmission, whereas agonists induce receptor desensitisation through excessive activation. The cellular basis for the latter lies in the fact that sustained activation triggers Ca^{2+} influx overload, altered phosphorylation and endocytosis-mediated degradation, ultimately leading to long-term functional inactivation of the receptor (152). Although their mechanisms are opposite, both can alleviate migraines, meaning there is no single primary mechanism (153).

To the best of our knowledge, no clinical trials have directly compared the relative efficacy of the two approaches. Existing evidence simply suggests that bidirectional modulation of the same target holds analgesic potential; however, neither approach has become an established therapy. Their clinical translation faces numerous challenges. Antagonist development is hampered by targeted side effects such as hyperthermia and impaired heat perception (154-156), while the desensitisation strategy of agonists, though capable of avoiding some side effects, notably increases the difficulty of clinical management due to the irritant response during the initial activation phase (73,157,158). Furthermore, the heterogeneity in TRPV1 expression and function across different disease courses, subtypes and comorbid conditions of migraine remains unclear, making it difficult to support the development of precision intervention strategies (159-161).

Future research directions. At a basic research level, in-depth analysis of the molecular mechanisms underlying TRPV1-mediated central sensitisation is necessary. The present review recommends use of single-cell sequencing technology to elucidate the subpopulation heterogeneity of TRPV1-positive neurons in the TNC region (162,163), generate cell-type-specific TRPV1 conditional knockout mice

to clarify the role of TRPV1 in different cell types in migraine chronicity (164) and to investigate cross-regulatory networks between TRPV1, glial cell activation and neuroinflammation to identify novel molecular targets for clinical research (165).

At the clinical research level, the focus is on developing novel TRPV1-targeted drugs with high selectivity and minimal side effects. To address the translational challenges associated with TRPV1 antagonists, future efforts should focus on developing modally selective or preferential antagonists. By modulating the conformational dynamics of the channel protein, such drugs can specifically block pain signalling pathways without interfering with thermoregulatory functions (166,167). Concurrently, adverse reactions can be reduced through structural modifications and targeted delivery systems, and partial agonists or preferential modulators can be explored to precisely regulate receptor activity (168). TRPV1 PET tracers should be developed for the non-invasive assessment of central sensitisation in patients (169,170). Research into personalised migraine treatment based on TRPV1 genotype or expression levels should also be pursued (171). Concurrently, large-scale, multicentre clinical trials are needed to validate the efficacy and safety of targeted drugs and advance their clinical translation.

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Authors' contributions

MZ was responsible for drafting the manuscript and creating the table and figure. YP and YZ provided key insights and contributed to the drafting of the manuscript. JH was responsible for literature searches, inclusion and exclusion criteria as well as literature organization and participated in the revision process. SL and HT refined the research concept and revised the final draft. BF and XB reviewed the manuscript and provided critical feedback. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

1. Olesen J: The international classification of headache disorders. 2nd edition (ICHD-II). Rev Neurol (Paris) 161: 689-691, 2005.
2. Dong L, Dong W, Jin Y, Jiang Y, Li Z and Yu D: The global burden of migraine: A 30-year trend review and future projections by age, sex, country, and region. Pain Ther 14: 297-315, 2025.
3. GBD 2016 Neurology Collaborators: Global, regional, and national burden of neurological disorders, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 18: 459-480, 2019.
4. Gasparini CF, Sutherland HG and Griffiths LR: Studies on the pathophysiology and genetic basis of migraine. Curr Genomics 14: 300-315, 2013.
5. Rosignoli C, Ornello R, Onofri A, Caponnetto V, Grazzi L, Raggi A, Leonardi M and Sacco S: Correction: Applying a biopsychosocial model to migraine: Rationale and clinical implications. J Headache Pain 23: 116, 2022.
6. Jayamurali D, Ravishankar N, Manoharan N, Parasuraman R, Jayashankar SK and Govindarajulu SN: Neuropeptide network of polycystic ovary syndrome-A review. Protein Pept Lett 31: 667-680, 2024.
7. Andreou AP and Edvinsson L: Mechanisms of migraine as a chronic evolutive condition. J Headache Pain 20: 117, 2019.
8. Dodick D and Silberstein S: Central sensitization theory of migraine: Clinical implications. Headache 46 (Suppl 4): S182-S191, 2006.
9. Woolf CJ: Central sensitization: Implications for the diagnosis and treatment of pain. Pain 152: (3 Suppl) S2-S15, 2011.
10. Burstein R and Jakubowski M: Analgesic triptan action in an animal model of intracranial pain: A race against the development of central sensitization. Ann Neurol 55: 27-36, 2004.
11. Noseda R and Burstein R: Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain 154 (Suppl 1): S44-S53, 2013.
12. Singh S and Bhatt LK: Targeting cellular senescence: A potential therapeutic approach for Alzheimer's disease. Curr Mol Pharmacol 17: e010623217543, 2024.
13. Wu LJ, Sweet TB and Clapham DE: International union of basic and clinical pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family. Pharmacol Rev 62: 381-404, 2010.
14. Chubanov V, Grimm C, Hill K, Schaefer M, Köttgen M, Storch U, Mederos Y, Schnitzler M, Kudrina V, Erbacher A and Gudermann T: Physiological functions and pharmacological targeting of transient receptor potential channels. Pharmacol Rev 77: 100089, 2025.
15. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD and Julius D: The capsaicin receptor: A heat-activated ion channel in the pain pathway. Nature 389: 816-824, 1997.
16. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI and Julius D: The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 21: 531-543, 1998.
17. Messlinger K, Balcziak LK and Russo AF: Cross-talk signaling in the trigeminal ganglion: Role of neuropeptides and other mediators. J Neural Transm (Vienna) 127: 431-444, 2020.
18. Lyu G and Li D: PLEKHG7 Expression: A biomarker for prognosis and targeted therapy in diffuse large B-cell lymphoma. Protein Pept Lett 32: 657-666, 2025.
19. Kim YS, Chu Y, Han L, Li M, Li Z, Lavinka PC, Sun S, Tang Z, Park K, Caterina MJ, *et al*: Central terminal sensitization of TRPV1 by descending serotonergic facilitation modulates chronic pain. Neuron 81: 873-887, 2014.
20. Tavares-Ferreira D, Shiers S, Ray PR, Wangzhou A, Jeevakumar V, Sankaranarayanan I, Cervantes AM, Reese JC, Chamessian A, Copits BA, *et al*: Spatial transcriptomics of dorsal root ganglia identifies molecular signatures of human nociceptors. Sci Transl Med 14: eabj8186, 2022.
21. Nugent FS and Kauer JA: LTP of GABAergic synapses in the ventral tegmental area and beyond. J Physiol 586: 1487-1493, 2008.

22. Chen J, Sun W, Zhu Y, Zhao F, Deng S, Tian M, Wang Y and Gong Y: TRPV1: The key bridge in neuroimmune interactions. J Intensive Med 4: 442-452, 2024.
23. Li J and Bian X: Optimizing sleep in athletes: The potential of α-Lactalbumin in nutrition intervention. Protein Pept Lett 32: 402-413, 2025.
24. Woolf CJ: Evidence for a central component of post-injury pain hypersensitivity. Nature 306: 686-688, 1983.
25. Ashina M, Terwindt GM, Al-Karagholi MA, De Boer I, Lee MJ, Hay DL, Schulte LH, Hadjikhani N, Sinclair AJ, Ashina H, *et al*: Migraine: Disease characterisation, biomarkers, and precision medicine. Lancet 2021; 397: 1496-1504, 2021.
26. Suzuki K, Suzuki S, Shiina T, Kobayashi S and Hirata K: Central sensitization in migraine: A narrative review. J Pain Res 15: 2673-2682, 2022.
27. Di Antonio S, Arendt-Nielsen L, Ponzano M, Bovis F, Torelli P, Finocchi C and Castaldo M: Trigeminocervical pain sensitivity during the migraine cycle depends on headache frequency. Neurol Sci 44: 4021-4032, 2023.
28. Rolke R, Baron R, Maier C, Tölle TR, Treede DR, Beyer A, Binder A, Birbaumer N, Birklein F, Bötefür IC, *et al*: Quantitative sensory testing in the German research network on neuropathic pain (DFNS): Standardized protocol and reference values. Pain 123: 231-243, 2006.
29. Van Welie FC, Dahan A, Van Velzen M and Terwindt GM: Pain profiling in migraine: A systematic review of Quantitative sensory testing (QST), conditioned pain modulation (CPM), and corneal confocal microscopy (CCM). J Headache Pain 25: 224, 2024.
30. Cnockaert E, Meeus M, Cagnie B, Chys M, Steverlynck C, Moerkerke M and Van Oosterwijck J: Human assumed central sensitization in interictal migraine: A systematic review and meta-analysis. Neurol Sci 47: 250, 2026.
31. Perrotta A: Pain processing in primary headaches, from spinal sensitisation to cortical modulation. J Headache Pain 16 (Suppl 1): A12, 2015.
32. Yanes JA: Toward a multimodal framework of brainstem pain-modulation circuits in migraine. J Neurosci 39: 6035-6037, 2019.
33. Youn DH, Gerber G and Sather WA: Ionotropic glutamate receptors and voltage-gated Ca²□ channels in long-term potentiation of spinal dorsal horn synapses and pain hypersensitivity. Neural Plast 2013: 654257, 2013.
34. Castaldo M, Arendt-Nielsen L, Ponzano M, Bovis F, Torelli P, Finocchi C and Di Antonio S: Cut-Off values able to identify migraine patients with increased pressure-pain sensitivity independent of the migraine cycle through a single assessment: A secondary analysis of a multicentre, cross-sectional, observational study. Eur J Pain 29: e4787, 2025.
35. Tohyama S, Datko M, Brusaferri L, Kinder LD, Schnieders JH, Hyman M, Goldstein AM, Gilbert MD, Housman H, Le V, *et al*: Trigeminal nerve microstructure is linked with neuroinflammation and brainstem activity in migraine. Brain 148: 2551-2562, 2025.
36. Kilinc E, Ankarali S, Torun IE and Dagistan Y: Receptor mechanisms mediating the anti-neuroinflammatory effects of endocannabinoid system modulation in a rat model of migraine. Eur J Neurosci 55: 1015-1031, 2022.
37. Fernandes EC, Carlos-Ferreira J, Luz LL and Safronov BV: Presynaptic interactions between trigeminal and cervical nociceptive afferents supplying upper cervical lamina I neurons. J Neurosci 42: 3587-3598, 2022.
38. Guerrero-Toro C, Koroleva K, Ermakova E, Gafurov O, Abushik P, Tavi P, Sitdikova G and Giniatullin R: Testing the role of glutamate NMDA receptors in peripheral trigeminal nociception implicated in migraine pain. Int J Mol Sci 23: 1529, 2022.
39. Supronsinchai W, Hoffmann J, Akerman S and Goadsby PJ: KCl-induced repetitive cortical spreading depression inhibiting trigeminal neuronal firing is mediated by 5-HT(1B/1D) and opioid receptors. Cephalalgia 42: 1339-1348, 2022.
40. Follansbee T, Le Chang H, Iodi Carstens M, Guan Y, Carstens E and Dong X: Optotagging and characterization of GABAergic rostral ventromedial medulla (RVM) neurons. Mol Pain 20: 17448069241270295, 2024.
41. Zhang KM, Wang XM, Peterson AM, Chen WY and Mokha SS: alpha2-adrenoceptors modulate NMDA-evoked responses of neurons in superficial and deeper dorsal horn of the medulla. J Neurophysiol 80: 2210-2214, 1998.
42. Mo SY, Xu XX, Bai SS, Liu Y, Fu KY, Sessle BJ, Cao Y and Xie QF: Neuronal activities in the rostral ventromedial medulla associated with experimental occlusal interference-induced orofacial hyperalgesia. J Neurosci 42: 5314-5329, 2022.
43. Mesa-Lombardo A, García-Magro N, Nuñez A and Martin YB: Impaired modulation of the trigeminal caudal nucleus by the locus coeruleus in diabetic mice: the role of GABAergic and glycinergic neurons. Front Neuroanat 19: 1600026, 2025.
44. Rogness VM, Juliette J, Khasabova IA, Gupta K, Khasabov SG and Simone DA: Descending facilitation of nociceptive transmission from the rostral ventromedial medulla contributes to hyperalgesia in mice with sickle cell disease. Neuroscience 526: 1-12, 2023.
45. De Preter CC and Heinricher MM: Direct and indirect nociceptive input from the trigeminal dorsal horn to pain-modulating neurons in the rostral ventromedial medulla. J Neurosci 43: 5779-5791, 2023.
46. Zheng F, Nixdorf-Bergweiler BE, Van Brederode J, Alzheimer C and Messlinger K: Excitatory effects of calcitonin gene-related peptide (CGRP) on superficial Sp5C neurons in mouse medullary slices. Int J Mol Sci 22: 3794, 2021.
47. Park S, Jung H, Han SW, Lee SH and Sohn JH: Differences in neuropathology between nitroglycerin-induced mouse models of episodic and chronic migraine. Int J Mol Sci 25: 3706, 2024.
48. Zhang X, Zhang W, Wang Y, Zhang Y, Zhang D, Qin G, Zhou J and Chen L: SIRT1-regulated ROS generation activates NMDAR2B phosphorylation to promote central sensitization and allodynia in a male chronic migraine rat model. Front Mol Neurosci 17: 1387481, 2024.
49. Martami F and Holton KF: Unmasking the relationship between CGRP and glutamate: From peripheral excitation to central sensitization in migraine. J Headache Pain 26: 101, 2025.
50. Liu RH, Zhang M, Xue M, Wang T, Lu JS, Li XH, Chen YX, Fan K, Shi W, Zhou SB, *et al*: Inhibiting neuronal AC1 for treating anxiety and headache in the animal model of migraine. iScience 26: 106790, 2023.
51. Xie W, Li R, Tang W, Ma Z, Miao S, Li C, Yang C, Li B, Wang T, Gong Z, *et al*: Proteomics profiling reveals mitochondrial damage in the thalamus in a mouse model of chronic migraine. J Headache Pain 24: 122, 2023.
52. Sowers LP, Wang M, Rea BJ, Taugher RJ, Kuburas A, Kim Y, Wemmie JA, Walker CS, Hay DL and Russo AF: Stimulation of posterior thalamic nuclei induces photophobic behavior in mice. Headache 60: 1961-1981, 2020.
53. Christensen RH, Al-Khazali HM, Melchior AG, Ashina M and Ashina H: Shared neural signatures of photophobia in migraine and post-traumatic headache: A task-based fMRI study. J Headache Pain 26: 154, 2025.
54. Nagata E, Takao M, Toriumi H, Suzuki M, Fujii N, Kohara S, Tsuda A, Nakayama T, Kadokura A and Hadano M: Hypersensitivity of intrinsically photosensitive retinal ganglion cells in migraine induces cortical spreading depression. Int J Mol Sci 25: 7980, 2024.
55. Zhang L, Zhou Y, Yang L, Wang Y and Xiao Z: PACAP6-38 improves nitroglycerin-induced central sensitization by modulating synaptic plasticity at the trigeminal nucleus caudalis in a male rat model of chronic migraine. J Headache Pain 24: 66, 2023.
56. Zhang C, Kaye JA, Cai Z, Wang Y, Prescott SL and Liberles SD: Area postrema cell types that mediate nausea-associated behaviors. Neuron 109: 461-472.e5, 2021.
57. Hoskin KL, Lambert GA, Donaldson C and Zagami AS: The 5-hydroxytryptamine1B/1D/1F receptor agonists eletriptan and naratriptan inhibit trigeminovascular input to the nucleus tractus solitarius in the cat. Brain Res 998: 91-99, 2004.
58. Zhang Y, Zhang Y, Wang Y, Zhang X, Qin G, Zhang D, Chen L and Zhou J: Inhibition of glutamatergic trigeminal nucleus caudalis-vestibular nucleus projection neurons attenuates vestibular dysfunction in the chronic-NTG model of migraine. J Headache Pain 24: 77, 2023.
59. Jin Z, Kim JB and Jin YH: Effect of endogenous substance P on visceral afferent signal integration in the nucleus tractus solitaries of rat brainstem slices. IBRO Neurosci Rep 15: 327-334, 2023.
60. Russo A, Silvestro M, Trojsi F, Bisecco A, De Micco R, Caiazzo G, Di Nardo F, Esposito F, Tessitore A and Tedeschi G: Cognitive networks disarrangement in patients with migraine predicts cutaneous allodynia. Headache 60: 1228-1243, 2020.

61. Hu J, Ji WJ, Liu GY, Su XH, Zhu JM, Hong Y, Xiong YF, Zhao YY, Li WP and Xie W: IDO1 modulates pain sensitivity and comorbid anxiety in chronic migraine through microglial activation and synaptic pruning. J Neuroinflammation 22: 42, 2025.
62. Kim YH, Back SK, Davies AJ, Jeong H, Jo HJ, Chung G, Na HS, Bae YC, Kim SJ, Kim JS, *et al*: TRPV1 in GABAergic interneurons mediates neuropathic mechanical allodynia and disinhibition of the nociceptive circuitry in the spinal cord. Neuron 74: 640-647, 2012.
63. Luo Y, Qiu Y, Zhou R, Zhang Y, Ji X, Liu Z, Li R, Zhang Y, Yang F, Hou J, *et al*: Shaoyao Gancao decoction alleviates the central hyperalgesia of recurrent NTG-induced migraine in rats by regulating the NGF/TRPV1/COX-2 signal pathway. J Ethnopharmacol 317: 116781, 2023.
64. Christiansen IM, Reducha PV, Edvinsson L, Holm A and Haanes KA: Ex vivo stimulation of the trigeminal nucleus caudalis induces peripheral CGRP release in the trigeminal ganglion and reveals a distinct dopamine-endocannabinoid mechanism relevant to migraine. J Headache Pain 26: 141, 2025.
65. Meza RC, Ancatén-González C, Chiu CQ and Chávez AE: Transient receptor potential vanilloid 1 function at central synapses in health and disease. Front Cell Neurosci 16: 864828, 2022.
66. Bejoma T, Pan Y and Zhao Q: TRPV1 from the TRP family: Structure, function, implication in autoimmune diseases and potential therapies. Channels (Austin) 20: 2616902, 2026.
67. Pumroy RA, Fluck EC III, Ahmed T and Moiseenkova-Bell VY: Structural insights into the gating mechanisms of TRPV channels. Cell Calcium 87: 102168, 2020.
68. Mobasheri A, Rannou F, Ivanavicius S and Conaghan PG: Targeting the TRPV1 pain pathway in osteoarthritis of the knee. Expert Opin Ther Targets 28: 843-856, 2024.
69. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R and Moskowitz MA: Migraine and the trigeminovascular system-40 years and counting. Lancet Neurol 18: 795-804, 2019.
70. Benemei S and Dussor G: TRP channels and migraine: Recent developments and new therapeutic opportunities. Pharmaceuticals (Basel) 12: 54, 2019.
71. Zeng X, Mai J, Xie H, Yang L and Liu X: Activation of CB1R alleviates central sensitization by regulating HCN2-pNR2B signaling in a chronic migraine rat model. J Headache Pain 24: 44, 2023.
72. Belinskaia M, Zurawski T, Kaza SK, Antoniazzi C, Dolly JO and Lawrence GW: NGF Enhances CGRP release evoked by capsaicin from rat trigeminal neurons: Differential inhibition by SNAP-25-cleaving proteases. Int J Mol Sci 23: 892, 2022.
73. Rosta J, Tóth M, Friedrich N, Sántha P, Jancsó G and Dux M: Insulin sensitizes neural and vascular TRPV1 receptors in the trigeminovascular system. J Headache Pain 23: 7, 2022.
74. De Logu F, Nassini R, Hegron A, Landini L, Jensen DD, Latorre R, Ding J, Marini M, Souza Monteiro De Araujo D, Ramírez-Garcia P, *et al*: Schwann cell endosome CGRP signals elicit periorbital mechanical allodynia in mice. Nat Commun 13: 646, 2022.
75. Greco R, Demartini C, Francavilla M, Zanaboni AM and Tassorelli C: Antagonism of CGRP receptor: Central and peripheral mechanisms and mediators in an animal model of chronic migraine. Cells 11: 3092, 2022.
76. Lu G, Xiao S, Meng F, Zhang L, Chang Y, Zhao J, Gao N, Su W, Guo X, Liu Y, *et al*: AMPK activation attenuates central sensitization in a recurrent nitroglycerin-induced chronic migraine mouse model by promoting microglial M2-type polarization. J Headache Pain 25: 29, 2024.
77. Citak A, Kilinc E, Torun IE, Ankarali S, Dagistan Y and Yoldas H: The effects of certain TRP channels and voltage-gated KCNQ/Kv7 channel opener retigabine on calcitonin gene-related peptide release in the trigeminovascular system. Cephalalgia 42: 1375-1386, 2022.
78. Li J, Cui Z, Gong H, Zhang Y, Yuan Z, Zhang Z, Ma Z, Zhou N, Huang C, Zhao Y, *et al*: Sleep deficiency exacerbates periodontal inflammation via trigeminal TRPV1 neurons. Proc Natl Acad Sci USA 122: e2424169122, 2025.
79. Wang Y, Yang S, Liu X, Chen C, Li Q, Wang X, Xu W, Gao J, Wang Y, Wang W and Wang T: Xiongshao Zhitong granules alleviate nitroglycerin-induced migraine by regulating the TRPV1-mediated NLRP3 inflammatory pathway in rats. Phytomedicine 142: 156754, 2025.
80. Bom AOP, Dias-Soares M, Corrêa RCD, Neves CL, Hosch NG, Lucena GG, Oliveira CG, Pagano RL, Chacur M and Giorgi R: Molecular aspects involved in the mechanisms of bothrops jararaca venom-induced hyperalgesia: Participation of NK1 receptor and glial cells. Toxins (Basel) 16: 187, 2024.
81. Johnson MB, Young AD and Marriott I: The therapeutic potential of targeting substance P/NK-1R interactions in inflammatory CNS disorders. Front Cell Neurosci 10: 296, 2016.
82. Gao YJ and Ji RR: Targeting astrocyte signaling for chronic pain. Neurotherapeutics 7: 482-493, 2010.
83. Chen H, Li G, Deng L, Xu N, Lee SM, Nie X and Bian JS: Identification and evaluation of a pinocembrin analog as a TRPV1 inhibitor with analgesic properties in murine pain models. Front Pharmacol 16: 1585181, 2025.
84. Kang SY, Seo SY, Bang SK, Cho SJ, Choi KH and Ryu Y: Inhibition of Spinal TRPV1 Reduces NMDA Receptor 2B phosphorylation and produces anti-nociceptive effects in mice with inflammatory pain. Int J Mol Sci 22: 11177, 2021.
85. Tamada M, Ohi Y, Kodama D, Miyazawa K, Goto S and Haji A: Modulation of excitatory synaptic transmissions by TRPV1 in the spinal trigeminal subnucleus caudalis neurons of neuropathic pain rats. Eur J Pharmacol 913: 174625, 2021.
86. Niu Y, Zeng X, Zhao L, Zhou Y, Qin G, Zhang D, Fu Q, Zhou J and Chen L: Metabotropic glutamate receptor 5 regulates synaptic plasticity in a chronic migraine rat model through the PKC/NR2B signal. J Headache Pain 21: 139, 2020.
87. Escobar-Espinal DM, Vivanco-Estela AN, Barros N, Dos Santos Pereira M, Guimaraes FS, Del Bel E and Nascimento GC: Cannabidiol and it fluorinate analog PECS-101 reduces hyperalgesia and allodynia in trigeminal neuralgia via TRPV1 receptors. Prog Neuropsychopharmacol Biol Psychiatry 132: 110996, 2024.
88. Moriyama H, Imoto H, Nomura S, Mori N, Maruta Y, Fujii N, Fujitsuku S and Ishihara H: TRPV1 antagonist AMG9810 suppresses focal epileptiform discharges and seizures by decreasing extracellular glutamate concentrations in mice. J Pharmacol Sci 159: 163-171, 2025.
89. Xu LL, Yan Y, Yuan YM, Li Y, Jiang J and Zhang LC: TRPV1 and GABA(B1) in the cerebrospinal fluid-contacting nucleus are jointly involved in chronic inflammatory pain in rats. J Pain Res 15: 3931-3939, 2022.
90. Ji NN, Meng QX, Wang Y, Zhou ZM, Song Y, Hua R and Zhang YM: Microglia-derived TNF-α inhibiting GABAergic neurons in the anterior lateral bed nucleus of the stria terminalis precipitates visceral hypersensitivity induced by colorectal distension in rats. Neurobiol Stress 18: 100449, 2022.
91. Zeng X, Niu Y, Qin G, Zhang D, Zhou J and Chen L: Deficiency in the function of inhibitory interneurons contributes to glutamate-associated central sensitization through GABABR2-SynCAM1 signaling in chronic migraine rats. FASEB J 34: 14780-14798, 2020.
92. Zhang Y, Ge F, Luo Y, Ji X, Liu Z, Qiu Y, Hou J, Zhou R, Zhao C, Xu Q, *et al*: Paeonol and glycyrrhizic acid in combination ameliorate the recurrent nitroglycerin-induced migraine-like phenotype in rats by regulating the GABBR2/TRPM8/PRKACA/TRPV1 pathway. J Ethnopharmacol 334: 118464, 2024.
93. Asaoka R, Ohi Y, Miyazawa K, Goto S and Haji A: Involvement of presynaptic TRPV1 channels in prostaglandin E(2)-induced facilitation of spontaneous synaptic transmission in the rat spinal trigeminal subnucleus caudalis. Brain Res 1715: 115-125, 2019.
94. Sun S, Fan Z, Liu X, Wang L and Ge Z: Microglia TREM1-mediated neuroinflammation contributes to central sensitization via the NF-κB pathway in a chronic migraine model. J Headache Pain 25: 3, 2024.
95. Jiang W, Feng XM, Yu P, Zhang LX, Cai MT, Qu K, Yang Y and Dong M: Asiaticoside alleviates migraine-induced cognitive impairment via TLR4-Mediated apoptosis regulation. Eur J Pharmacol 1007: 178204, 2025.
96. Zhang SS, Liu M, Liu DN, Yang YL, Du GH and Wang YH: TLR4-IN-C34 inhibits lipopolysaccharide-stimulated inflammatory responses via downregulating TLR4/MyD88/NF-κB/NLRP3 signaling pathway and reducing ROS generation in BV2 cells. Inflammation 45: 838-850, 2022.
97. Slepicka J and Palecek J: Glial activation enhances spinal TRPV1 receptor sensitivity in a paclitaxel model of neuropathic pain. Physiol Res 74: 677-691, 2025.
98. Ma YQ, Hu QQ, Kang YR, Ma LQ, Qu SY, Wang HZ, Zheng YM, Li SY, Shao XM, Li XY, *et al*: Electroacupuncture alleviates diabetic neuropathic pain and downregulates p-PKC and TRPV1 in dorsal root ganglions and spinal cord dorsal horn. Evid Based Complement Alternat Med 2023: 3333563, 2023.

99. Chen CC, Ke CH, Wu CH, Lee HF, Chao Y, Tsai MC, Shyue SK and Chen SF: Transient receptor potential vanilloid 1 inhibition reduces brain damage by suppressing neuronal apoptosis after intracerebral hemorrhage. Brain Pathol 34: e13244, 2024.
100. Lee WS, Kang JH, Lee JH, Kim YS, Kim JJ, Kim HS, Kim HW, Shin US and Yoon BE: Improved gliotransmission by increasing intracellular Ca(2+) via TRPV1 on multi-walled carbon nanotube platforms. J Nanobiotechnology 20: 367, 2022.
101. Hou Y, Yang Y, Zhao Z, Wang S, Chen X, Xie Y, Chen H and Xu J: Capsazepine inhibits astrocyte activation and attenuates neuroinflammation by targeting syntaxin 7. FASEB J 39: e70657, 2025.
102. Wei D, Birla H, Dou Y, Mei Y, Huo X, Whitehead V, Osei-Owusu P, Feske S, Patafio G, Tao Y and Hu H: PGE2 potentiates orai1-mediated calcium entry contributing to peripheral sensitization. J Neurosci 44: e0329232023, 2024.
103. Lin K, Fu D, Wang Z, Zhang X and Zhu C: Analgesic and anti-inflammatory effects of galangin: A potential pathway to inhibit transient receptor potential vanilloid 1 receptor activation. Korean J Pain 37: 151-163, 2024.
104. Chen F, Hao K, Shu C, Xiong Y, Xu R, Huang H, Peng B, Liu Z, Reynolds GP, Wang G and Wang H: TRPV1 suppresses microglial inflammatory activation to ameliorate schizophrenia-associated behaviors in maternal separation rats. Schizophr Bull: Sep 11, 2025 (Epub ahead of print).
105. Meng J, Qiu S, Zhang L, You M, Xing H and Zhu J: Berberine alleviate cisplatin-induced peripheral neuropathy by modulating inflammation signal via TRPV1. Front Pharmacol 12: 774795, 2021.
106. Hu J, Fan W, Xu Y, Li X, Zhang H, Li S and Xue L: Maladaptive changes in the homeostasis of AEA-TRPV1/CB1R induces pain-related hyperactivity of nociceptors after spinal cord injury. Cell Biosci 15: 2, 2025.
107. Zhu Z, Jiang Y, Li Z, Du Y, Chen Q, Guo Q, Ban Y and Gong P: Sensory neuron transient receptor potential vanilloid-1 channel regulates angiogenesis through CGRP in vivo. Front Bioeng Biotechnol 12: 1338504, 2024.
108. Peters JH, Mcdougall SJ, Fawley JA, Smith SM and Andresen MC: Primary afferent activation of thermosensitive TRPV1 triggers asynchronous glutamate release at central neurons. Neuron 65: 657-669, 2010.
109. Zhang Y and Wang Y: TRPV1: An important molecule involved in the peripheral sensitization during chronic pain and central pain modulation. Sheng Li Xue Bao 69: 677-684, 2017 (In Chinese).
110. Medvedeva YV, Kim MS and Usachev YM: Mechanisms of prolonged presynaptic Ca2+ signaling and glutamate release induced by TRPV1 activation in rat sensory neurons. J Neurosci 28: 5295-5311, 2008.
111. Notartomaso S, Scarselli P, Mascio G, Liberatore F, Mazzon E, Mammana S, Gugliandolo A, Cruccu G, Bruno V, Nicoletti F and Battaglia G: N-Acetylcysteine causes analgesia in a mouse model of painful diabetic neuropathy. Mol Pain 16: 1744806920904292, 2020.
112. Chen SR, Chen H, Jin D and Pan HL: Brief opioid exposure paradoxically augments primary afferent input to spinal excitatory neurons via α2δ-1-Dependent presynaptic NMDA receptors. J Neurosci 42: 9315-9329, 2022.
113. Barria A, Derkach V and Soderling T: Identification of the Ca2+/calmodulin-dependent protein kinase II regulatory phosphorylation site in the alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate-type glutamate receptor. J Biol Chem 272: 32727-32730, 1997.
114. Lee HK, Barbarosie M, Kameyama K, Bear MF and Huganir RL: Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. Nature 405: 955-959, 2000.
115. Liu Y, Yang H, Fu Y, Pan Z, Qiu F, Xu Y, Yang X, Chen Q, Ma D and Liu Z: TRPV1 antagonist prevents neonatal sevoflurane-induced synaptic abnormality and cognitive impairment in mice through regulating the Src/Cofilin signaling pathway. Front Cell Dev Biol 9: 684516, 2021.
116. Brewer CL and Kauer JA: Low-frequency stimulation of Trpv1-Lineage peripheral afferents potentiates the excitability of spino-periaqueductal gray projection neurons. J Neurosci 44: e1184232023, 2024.
117. Ivanova EA, Matyushkin AI and Voronina TA: Analysis of the involvement of NMDA receptors in analgesia and hypothermia induced by the activation of TRPV1 Ion channels. Acta Naturae 15: 42-50, 2023.
118. Kleeberg-Hartmann J, Vogler B and Messlinger K: Petasin and isopetasin reduce CGRP release from trigeminal afferents indicating an inhibitory effect on TRPA1 and TRPV1 receptor channels. J Headache Pain 22: 23, 2021.
119. Meents JE, Hoffmann J, Chaplan SR, Neeb L, Schuh-Hofer S, Wickenden A and Reuter U: Two TRPV1 receptor antagonists are effective in two different experimental models of migraine. J Headache Pain 16: 57, 2015.
120. Fan J, Ke H, Lei J, Wang J, Tominaga M and Lei X: Structural basis of TRPV1 inhibition by SAF312 and cholesterol. Nat Commun 15: 6689, 2024.
121. Go EJ, Hwang SM, Jo H, Rahman MM, Park J, Lee JY, Jo YY, Lee BG, Jung Y, Berta T, *et al*: GLP-1 and its derived peptides mediate pain relief through direct TRPV1 inhibition without affecting thermoregulation. Exp Mol Med 56: 2449-2464, 2024.
122. Kang JM, Kwon SO, Ann J, Lee S, Kim C, Do N, Jeong JJ, Blumberg PM, Ha H, Vu TNL, *et al*: 2-(Halogenated Phenyl) acetamides and propanamides as potent TRPV1 antagonists. Bioorg Med Chem Lett 48: 128266, 2021.
123. Lehto SG, Tamir R, Deng H, Klionsky L, Kuang R, Le A, Lee D, Louis JC, Magal E, Manning BH, *et al*: Antihyperalgesic effects of (R,E)-N-(2-hydroxy-2,3-dihydro-1H-inden-4-yl)-3-(2-(piperidin-1-yl)-4-(trifluoromethyl)phenyl)-acrylamide (AMG8562), a novel transient receptor potential vanilloid type 1 modulator that does not cause hyperthermia in rats. J Pharmacol Exp Ther 326: 218-229, 2008.
124. Summ O, Holland PR, Akerman S and Goadsby PJ: TRPV1 receptor blockade is ineffective in different in vivo models of migraine. Cephalalgia 31: 172-180, 2011.
125. Yue WWS, Yuan L, Braz JM, Basbaum AI and Julius D: TRPV1 drugs alter core body temperature via central projections of primary afferent sensory neurons. Elife 11: e80139, 2022.
126. Garami A, Steiner AA, Pakai E, Wanner SP, Almeida MC, Keringer P, Oliveira DL, Nakamura K, Morrison SF and Romanovsky AA: The neural pathway of the hyperthermic response to antagonists of the transient receptor potential vanilloid-1 channel. Temperature (Austin) 10: 136-154, 2023.
127. Costa RF, Rosas EP, Paz ST, Freitas MFL, Souza SL, Andrade JR, Oliveira DA, Jansen-Olesen I, Christensen SL and Valença MM: Topiramate inhibits capsaicin-induced mast cell degranulation and CGRP release in rat dura mater. Brain Sci 14: 1070, 2024.
128. Deng SY, Tang XC, Chang YC, Xu ZZ, Chen QY, Cao N, Kong LJ, Wang Y, Ma KT, Li L and Si JQ: Improving nkcc1 function increases the excitability of DRG neurons exacerbating pain induced after TRPV1 activation of primary sensory neurons. Front Cell Neurosci 15: 665596, 2021.
129. Mcarthur JR, Finol-Urdaneta RK and Adams DJ: Analgesic transient receptor potential vanilloid-1-active compounds inhibit native and recombinant T-type calcium channels. Br J Pharmacol 176: 2264-2278, 2019.
130. Krivoshein G, Della Pietra A, Savinainen J, Van Den Maagdenberg AMJM and Giniatullin R: Differential inhibitory effects of endocannabinoids on neuronal firing of mouse meningeal afferents. J Headache Pain 26: 112, 2025.
131. Choi H and Goldman JD: High-concentration capsaicin topical system for painful diabetic peripheral neuropathy. Clin Diabetes 43: 165-168, 2024.
132. Überall MA, Sabatowski R, Lux MP, Heine M, Garcia Guerra L, Eerdekens M and Quandel T: Real-world 12-month outcomes of repeated high-concentration capsaicin patch in chemotherapy-induced peripheral neuropathy: Results from the CASPAR study. Front Oncol 15: 1711597, 2025.
133. Zhao Y, Zhang H, Wang Z, Zhu M, Zhang X and Zhang D: PTPRK promotes resiniferatoxin-induced postherpetic neuralgia via activating DUSP1/p38 MAPK signaling pathway in dorsal root ganglia. Sci Rep 15: 40630, 2025.
134. Craft RM and Porreca F: Tetracaine attenuates irritancy without attenuating desensitization produced by intravesical resiniferatoxin in the rat. Pain 57: 351-359, 1994.
135. Szallasi A: Resiniferatoxin: Nature's precision medicine to silence TRPV1-Positive afferents. Int J Mol Sci 24: 15042, 2023.
136. Alsalem M, Aldossary SA, Haddad M, Altarifi A, Kalbouneh H, Azab B, Mustafa AG, Jaffal SM and El-Salem K: The desensitization of the transient receptor potential vanilloid 1 by nonpungent agonists and its resensitization by bradykinin. Neuroreport 31: 781-786, 2020.
137. Cheng XL, Ruan YL, Dai JY, Fan HZ, Ling JY, Chen J, Lu WG, Gao XJ and Cao P: 8-shogaol derived from dietary ginger alleviated acute and inflammatory pain by targeting TRPV1. Phytomedicine 128: 155500, 2024.

138. Dong L, Zhou Q, Liang Q, Qiao Z, Liu Y, Shao L and Wang K: Identification of a partial and selective TRPV1 agonist CPIPC for alleviation of inflammatory pain. Molecules 27: 5428, 2022.
139. Ghosh K, Huang Y, Jin D, Chen SR and Pan HL: Histone methyltransferase G9a in primary sensory neurons promotes inflammatory pain and transcription of Trpa1 and Trpv1 via bivalent histone modifications. J Neurosci 45: e1790242024, 2025.
140. Bai G, Ross H, Zhang Y, Lee K and Ro JY: The Role of DNA methylation in transcriptional regulation of pro-nociceptive genes in rat trigeminal ganglia. Epigenet Insights 13: 2516865720938677, 2020.
141. Lai CY, Hsieh MC, Chou D, Lin KH, Wang HH, Yang PS, Lin TB and Peng HY: The transcription factor Tbx5-Dependent epigenetic modification contributes to neuropathic allodynia by activating TRPV1 expression in the dorsal horn. J Neurosci 44: e0497242024, 2024.
142. Price E, Gianfrancesco O, Harrison PT, Frank B, Bubb VJ and Quinn JP: CRISPR deletion of a SVA retrotransposon demonstrates function as a cis-Regulatory element at the TRPV1/TRPV3 intergenic region. Int J Mol Sci 22: 1911, 2021.
143. Wen Q, Wang Y, Pan Q, Tian R, Zhang D, Qin G, Zhou J and Chen L: MicroRNA-155-5p promotes neuroinflammation and central sensitization via inhibiting SIRT1 in a nitroglycerin-induced chronic migraine mouse model. J Neuroinflammation 18: 287, 2021.
144. Li Z, Li Y and Li Z: Low-Level miR-199 contribute to neuropathic low back pain via TRPV1 by regulating the production of pro-inflammatory cytokines on macrophage. Turk Neurosurg 34: 299-307, 2024.
145. Li Z, Zhou Y and Li Z: NFKB1 Signalling Activation Contributes to TRPV1 Over-expression via Repressing MiR-375 and MiR-455: A study on neuropathic low back pain. Folia Biol (Praha) 68: 105-111, 2022.
146. Zhang Y, Zhang M, Tang C, Hu J, Cheng X, Li Y, Chen Z, Yin Y, Xie C, Li D and Yao J: Palmitoylation by ZDHHC4 inhibits TRPV1-mediated nociception. EMBO Rep 26: 101-121, 2025.
147. Berg T, Metzner K, Bahrami N, Wang E, Koch M, Eaton P, Schmidtko A and Kallenborn-Gerhardt W: Redox-dependent activation of protein kinase G1α contributes to transient receptor potential cation channel subfamily V member 1-mediated acute nociceptive pain behavior. Redox Rep 30: 1-17, 2025.
148. Tanaka M, Tuka B and Vécsei L: Navigating the neurobiology of migraine: From pathways to potential therapies. Cells 13: 1098, 2024.
149. Zhou M, Pang F, Liao D, Yang Y, Wang Y, Yang Z, He X and Tang C: Electroacupuncture improves allodynia and central sensitization via modulation of microglial activation associated P2X4R and inflammation in a rat model of migraine. Mol Pain 20: 17448069241258113, 2024.
150. Akerman S, Karsan N, Bose P, Hoffmann JR, Holland PR, Romero-Reyes M and Goadsby PJ: Nitroglycerine triggers triptan-responsive cranial allodynia and trigeminal neuronal hypersensitivity. Brain 142: 103-119, 2019.
151. Sureda-Gibert P, Romero-Reyes M and Akerman S: Nitroglycerin as a model of migraine: Clinical and preclinical review. Neurobiol Pain 12: 100105, 2022.
152. Sanz-Salvador L, Andrés-Borderia A, Ferrer-Montiel A and Planells-Cases R: Agonist- and Ca2+-dependent desensitization of TRPV1 channel targets the receptor to lysosomes for degradation. J Biol Chem 287: 19462-19471, 2012.
153. Holzer P: The pharmacological challenge to tame the transient receptor potential vanilloid-1 (TRPV1) nocisensor. Br J Pharmacol 155: 1145-1162, 2008.
154. Gao YH, Huang YZ, Li ZX, Chen XY, Shao CY, Li HW, Liu B, Yang F, Chen MR, Lu ML, *et al*: Structures of TRPV1 bound by hyperthermia-inducing analgesics. Cell Rep 45: 116765, 2026.
155. Stasi K, Alshare Q, Jain M, Wald M and Li Y: Topical ocular TRPV1 Antagonist SAF312 (Libvatrep) demonstrates safety, low systemic exposure, and no anesthetic effect in healthy participants. Transl Vis Sci Technol 11: 15, 2022.
156. Brandt MR, Beyer CE and Stahl SM: TRPV1 antagonists and chronic pain: Beyond thermal perception. Pharmaceuticals (Basel) 5: 114-132, 2012.
157. Jiang Z, Li A, Luo W, Luo X, Liang D, Li J, Tang K, Liu L, Long Z, Miao R, *et al*: Targeting TRPV1 channels in desensitized neural afferent pathways may help mitigate pain and lower urinary tract symptoms caused by prostatitis. Front Pharmacol 16: 1541684, 2025.
158. Tian Q, Hu J, Xie C, Mei K, Pham C, Mo X, Hepp R, Soares S, Nothias F, Wang Y, *et al*: Recovery from tachyphylaxis of TRPV1 coincides with recycling to the surface membrane. Proc Natl Acad Sci USA 116: 5170-5175, 2019.
159. Giacon M, Cargnin S, Allena M, Greco R, Zanaboni AM, Facchetti S, De Icco R, Sances G, Ghiotto N, Guaschino E, *et al*: Lack of association between TRPV1 gene polymorphisms and risk of migraine chronification: A case-control study and meta-analysis. Neurol Sci 46: 303-312, 2025.
160. Wang M, Gu Y, Meng S, Kang L, Yang J, Sun D, Liu Y, Wan Z, Shan Y, Xue D, *et al*: Association between TRP channels and glutamatergic synapse gene polymorphisms and migraine and the comorbidities anxiety and depression in a Chinese population. Front Genet 14: 1158028, 2023.
161. Togha M, Ghorbani Z, Ramazi S, Zavvari F and Karimzadeh F: Evaluation of serum levels of transient receptor potential cation channel subfamily V Member 1, Vasoactive intestinal polypeptide, and pituitary adenylate cyclase-activating polypeptide in chronic and episodic migraine: The possible role in migraine transformation. Front Neurol 12: 770980, 2021.
162. Hu S, Tang Z, Sun S, Liu L, Wang Y, Xu L, Yuan J, Chen Y, Sun M and Zhao L: Single-Nucleus transcriptomics reveals glial metabolic-immune rewiring and intercellular signaling disruption in chronic migraine. Biomolecules 15: 942, 2025.
163. Nguyen MQ, Wu Y, Bonilla LS, Von Buchholtz LJ and Ryba NJP: Diversity amongst trigeminal neurons revealed by high throughput single cell sequencing. PLoS One 12: e0185543, 2017.
164. He S, Zambelli VO, Sinharoy P, Brabenec L, Bian Y, Rwere F, Hell RC, Stein Neto B, Hung B, Yu X, *et al*: A human TRPV1 genetic variant within the channel gating domain regulates pain sensitivity in rodents. J Clin Invest 133: e163735, 2023.
165. Zhang K, Qin Z, Chen J, Guo G, Jiang X, Wang F, Zhuang J and Zhang Z: TRPV1 modulated NLRP3 inflammasome activation via calcium in experimental subarachnoid hemorrhage. Aging (Albany NY) 16: 1096-1110, 2024
166. Daniluk J and Voets T: pH-dependent modulation of TRPV1 by modality-selective antagonists. Br J Pharmacol 180: 2750-2761, 2023.
167. Garami A, Shimansky YP, Rumbus Z, Vizin RCL, Farkas N, Hegyi J, Szakacs Z, Solymar M, Csenkey A, Chiche DA, *et al*: Hyperthermia induced by transient receptor potential vanilloid-1 (TRPV1) antagonists in human clinical trials: Insights from mathematical modeling and meta-analysis. Pharmacol Ther 208: 107474, 2020.
168. Huang YZ, Ma JX, Bian YJ, Bai QR, Gao YH, Di SK, Lei YT, Yang H, Yang XN, Shao CY, *et al*: TRPV1 analgesics disturb core body temperature via a biased allosteric mechanism involving conformations distinct from that for nociception. Neuron 112: 1815-1831.e4, 2024.
169. Tateishi U and Doi H: Transient receptor potential cation channel subfamily V member 1 (TRPV1) targeted PET imaging. Jpn J Clin Oncol 54: 386-394, 2024.
170. Marino S, Jassar H, Kim DJ, Lim M, Nascimento TD, Dinov ID, Koeppe RA and Dasilva AF: Classifying migraine using PET compressive big data analytics of brain's μ-opioid and D2/D3 dopamine neurotransmission. Front Pharmacol 14: 1173596, 2023.
171. Ahlatcı A, Yıldızhan K, Keleş ÖF, Bayir MH and Çınar R: The effect of hesperidin on trigeminal nerve damage in an NTG-induced migraine model: the role of the TRPV1 channel. Mol Biol Rep 53: 25, 2025.