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The Role of Mechanosensitive Piezo Channels in Chronic Pain

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Purpose of Review: Mechanosensitive Piezo channels are ion channels activated by mechanical stimuli, playing a crucial role in mechanotransduction processes and mechanical hypersensitivity. When these channels are subjected to mechanical loading, membrane currents rise instantaneously, depolarizing and activating voltage-gated calcium channels. This results in an increase in intracellular Ca^{2+}, which contributes to heightened sensitivity to mechanical stimuli. This review delves into the characteristics and mechanisms of Piezo channels in chronic pain.

Recent Findings: The findings suggest that Piezo channels are integral to the occurrence and development of chronic pain, including neuropathic pain, visceral pain, musculoskeletal pain, headache or orofacial pain, and inflammatory pain. Piezo channels significantly impact pain perception and transmission. These channels' critical involvement in various pain types highlights their potential as promising targets for chronic pain therapy.

Summary: This review discusses the role of Piezo channels in chronic pain. By understanding these pain mechanisms, new therapeutic strategies can be developed to alleviate chronic pain, offering hope for patients suffering from these debilitating conditions.

Keywords: Piezo channel, mechanotransduction, mechanical hypersensitivity, chronic pain

Introduction

Chronic pain is a widespread health issue that causes significant suffering and disability, characterized by its persistence or recurrence for over three months.[1] Approximately 20% of the global population is affected by chronic pain,[2] with more than 300 million individuals affected in China alone.[3] Chronic pain not only results in physical discomfort but also contributes to sleep disturbances, reduced appetite, psychological distress, and a heightened risk of suicide, profoundly diminishing overall quality of life.[4] Despite the availability of various clinical treatments, including opioids, nonsteroidal anti-inflammatory drugs, antidepressants, and traditional Chinese therapies, no perfect solution exists, as these options are often limited in effectiveness and may cause adverse effects.[5] Therefore, exploring the molecular mechanisms underlying chronic pain to identify new therapeutic targets remains crucial.

Various environmental factors, including chemical stimuli, electrical stimuli, heat, and changes in pH, influence cell activity. Specific receptors on the cell surface interact with these stimuli, initiating cellular signaling pathways and a series of physiological responses, such as alterations in metabolic activity and cell morphology.[6] For instance, neurotransmitters released at the axon terminals of neurons can bind to receptors on the postsynaptic membrane, generating electrical signals that activate downstream neurons or muscle cells.[7] Additionally, mechanical stimulation is also an essential factor in cellular sensory responses. Cells are exposed to physical forces such as tension, compression, gravity, shear stress, or pressure, which regulate cellular volume, migration, and differentiation.[8] Mechanosensitive ion

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channels, which act as the primary mechanical sensors on the cell surface, directly detect mechanical stimuli applied to the cell membrane, leading to membrane excitation or intracellular signal activation.[9,10]

Various mechanosensitive ion channels are involved in sensing and responding to mechanical stimulation, including epithelial sodium channel proteins (ENaC), Piezo channel family, TREK subfamily proteins, transient receptor potential (TRP) family proteins, and transmembrane protein 16 (TMEM16) superfamily.[8] The Piezo mechanotransduction channel family, first identified in 2010, has attracted significant attention in mechanobiology due to its distinctive properties and functions.[9] Its activation in response to mechanical stimuli leads to the transmembrane transport of positive ions into the cell, converting mechanical signals into electrochemical signals. This process involves various mechanotransduction functions, including touch perception and proprioception, as well as cell division, proliferation, differentiation, and migration.[11–13] Additionally, the activation of mechanosensitive ion channels is linked to the sensory transduction of nociception in both sensory neurons and non-neuron cells.[14]

Recent studies have clarified the involvement of Piezo channels in various chronic pain disorders, including neuropathic pain, visceral pain, musculoskeletal pain, headache, and orofacial pain. This review will examine the mechanisms by which Piezo channels contribute to these pain conditions. Targeting these ion channels may provide a novel therapeutic approach to managing chronic pain.

Properties and the Expression Profiles of Piezo Channels

Characteristics of Piezo Channels

Piezo channels consist of proteins that are approximately 2500 amino acids in length, each monomer containing up to 38 transmembrane segments. These channels are unique because they exhibit no homology to other known proteins. The molecular structure of Piezo1 was revealed in 2015 using cryo-electron microscopy. It is structured like the "propellers" of a helicopter, with the C-terminal pore in between (Figure 1).[15] High-resolution cryo-electron microscopy further confirmed that Piezo1 forms a massive "three-bladed peripheral structure", interconnected by intracellular beams, each about 90 Å long. The central pore formed by the C-terminal regions is crucial for the channel's ion conductance and selectivity.[16] Piezo2 has been shown to undergo extensive alternative splicing, generating multiple isoforms with distinct functional properties. While many Piezo2 isoforms are enriched in sensory neurons, non-neuronal tissues predominantly express a single isoform. These alternative splicing events modify key characteristics of Piezo2, such as their inactivation rates, ion permeability, and modulation by intracellular calcium. This splicing-driven diversity plays a crucial role in the specialization of mechanosensory functions, allowing Piezo2 to adapt to the specific needs of different cell types and tissues.[17]

When subjected to mechanical stimuli that occur in discrete steps, Piezo channels swiftly open in a manner dependent on the intensity of the stimulus and then rapidly inactivate, entering a non-conducting state within a few tens of milliseconds.[9] While the detailed molecular mechanisms responsible for this inactivation are not fully understood, several factors such as local pH fluctuations, concentrations of divalent ions, transmembrane voltage, resting membrane tension, and the activity of G protein-coupled pathways may play a role in influencing this process.[18] Piezo1 exhibits low efficiency in transducing continuous high-frequency mechanical stimuli, with activation efficiencies ranging between 10% and 71% for sinusoidal stimuli and 10% and 24% for continuous stimulation, demonstrating their limited ability to discern sustained stimuli.[18]

A comparison between the Piezo1 and Piezo2 subtypes revealed that Piezo2 channels exhibit faster kinetics and tend to mediate more rapid membrane responses. In contrast, Piezo1 channels show slower kinetics.[9] Piezo2 is primarily involved in detecting transient mechanical forces, while Piezo1 is capable of responding to prolonged mechanical activation (Table 1). [18]

Activation of Piezo Channels

There are currently two models explaining how mechanical forces mediate the switching of mechanosensitive ion channels from a closed to an open state. The first is the membrane tension model, which proposes that mechanical force applied to the lipid bilayer creates tension that subsequently gates the channel. In contrast, the tether model

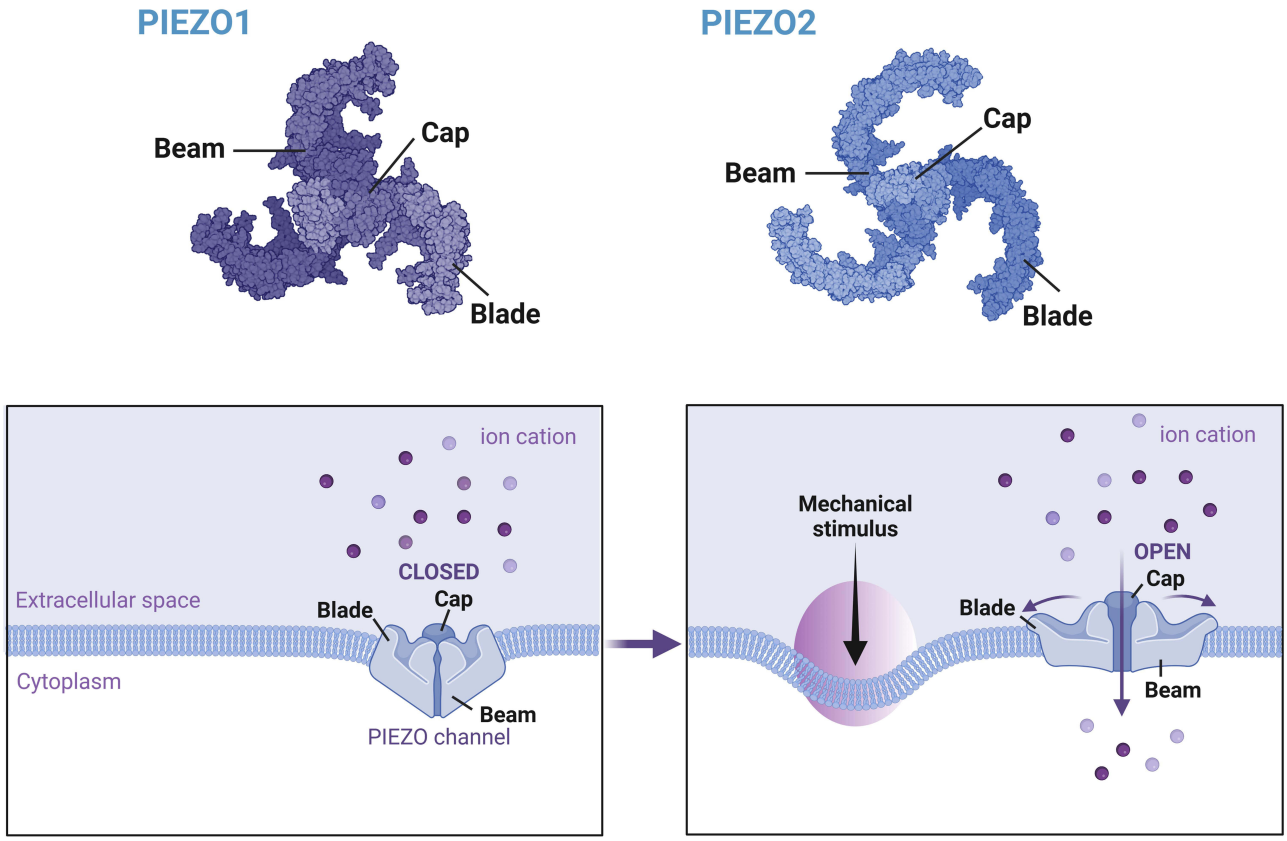

Figure 1 The structure and function of Piezo channels. Both Piezo1 and Piezo2 have a three-bladed, propeller-like structure. Both are homotrimeric- The three subunits come together to form the central membrane-spanning pore. Piezo1 and Piezo2 are both mechanically activated cation channels. Based on protein structure, it was predicted that the "blades" of the Piezo channels undergo a lever-like flattening motion upon application of mechanical stress. This opens their central pore, allowing an influx of positive charge. Created in BioRender. Wan, Y. (2024) https://BioRender.com/c34h896.

suggests that mechanical forces applied to the cell or extracellular matrix are transmitted by a protein "rope" linking the channel to membrane elements, thus leading to channel gating. The critical difference between these models lies in whether additional components are required to facilitate the conformational shift.[8] Researchers hypothesized that when a force is applied to the cell membrane, changes in membrane tension cause the Piezo channel to deform from curved to flat, expanding the flat membrane area and driving the opening of the channel.[15] In recent research, scientists proposed a force-from-filaments or tether model of Piezo channels based on Cadherin-mediated cytoskeletal structures. They found that Piezo channels could bind to F-actin via the cadherin-β-catenin mechanical sensing complex, establishing a connection to the cytoskeleton and sensing mechanical force changes throughout the cell transmitted by the cytoskeleton.[19] They discover that at the molecular level, the extracellular region of E-Cadherin interacts directly with

Table 1 The Difference in Characteristics of Piezo1 and Piezo2

Characteristics	Piezo1	Piezo2
Kinetics	Slower ($10 < \tau_{inac} < 30$ ms and $\tau_{inac} > 30$ ms)	Faster (τ_{inac}<10 ms)
Response to mechanical forces	Detection of more persistent mechanical forces	Detection of transient mechanical forces
expression	Mainly in nonneuronal cells, ie keratinocyte, Schwann cells	Mainly in DRG neurons
Sense	Sense membrane tension	Sense membrane curvature
Participate in physiological processes	Involved in embryonic vascular maturation, blood pressure regulation, urinary osmoregulation, epithelial homeostasis	Involved in the sensation of gentle touch, proprioception, tactile allodynia, airway stretch, and lung inflation

Note: τ_{inac}: The calculated time constants for inactivation.

the cap domain of Piezo1. In contrast, its intracellular domain interacts directly with the intracellular gated element of Piezo1, facilitating the direct focus of cytoskeleton-mediated mechanical forces on the critical mechano-gated functional domain of the Piezo channel.[19]

Distribution Profiles in Pain Regulation Pathway

Piezo1, predominantly found in non-neuronal cells, is essential in various physiological processes. These include the maturation of embryonic blood vessels,[20] regulation of blood pressure,[21] control of urinary osmoregulation,[22] maintenance of epithelial homeostasis,[23] guidance of axonal development, and determination of neural stem cell fate,[24] On the contrary, Piezo2 is mainly located in dorsal root ganglion (DRG) neurons.[25] It is critical for sensory functions, such as gentle touch perception,[11] proprioceptive feedback,[26] and tactile allodynia.[27] These differences in localization and function highlight Piezo channels' distinct but complementary roles in the body.

Piezo2 is expressed across neurons of all sizes in both human and mouse DRG, including large-diameter neurons responsible for detecting mechanical forces involved in proprioception, touch, and mechanical pain.[11,28] However, the expression of Piezo channel subtypes in nociceptive neurons remains a subject of debate. One study reported evidence for the presence of both Piezo1 and Piezo2 in DRG neurons,[29] revealing that Piezo1 is selectively expressed in 60% of rat DRG primary sensory neurons, with a higher concentration of immunoreactivity in small- and medium-sized neurons, contributing to mechanical pain and sensitivity.[29] Piezo1 immunoreactivity was also identified in perineuronal glial cells within the DRG, including satellite glial cells (SGCs) and Schwann cells. Furthermore, Piezo1 expression was observed in Schwann cells around axons in the sciatic nerve, cutaneous afferent endings, skin epidermal Merkel cells, and melanocytes.[30] Although research has shown that Piezo2 in sensory neurons plays either no inhibitory role[11] or only a partial[30,31] role in the detection of mechanical sensitivity, its roles in tactile allodynia[11,27,32,33] and visceral pain[34] are crucial. Mutations in the Piezo2 channel significantly increase the sensitivity of nociceptive receptors to mechanical stimuli. Relieving the voltage block of the Piezo2 ion channel can lead to sustained activity and sensitization of these receptors.[35] These findings highlight the critical involvement of Piezo channels in peripheral pain mechanisms (Figure 2).

In the central nervous system, mechanically gated Piezo ion channels play a vital role in regulating neural stem cell differentiation,[36] cell migration,[37] axon guidance,[12] and oligodendrocyte-mediated axonal myelination.[12] Notably, pharmacological activation of Piezo1 has been shown to cause demyelination, while inhibition of mechanosensitive channels, such as the application of the spider venom toxin GsMTx4, could potentially reduce neurodegeneration in the later stages of demyelinating diseases.[12] Furthermore, Piezo1 channels, when activated by mechanical forces, trigger Ca^{2+} signaling in capillary endothelial cells, indicating their role as capillary mechanosensors that influence blood flow regulation within the central nervous system (Figure 2).[38]

Roles in Nociception

Roles in Mechanical Pain

Mechanical pain is caused by mechanical stimuli such as cutting, compression, and stretching. Sensory neurons, known as low-threshold mechanoreceptors and nociceptors, are responsible for detecting innocuous and noxious mechanical stimuli, respectively.[39] Piezo channels are a type of mechanosensitive ion channel that is highly sensitive to mechanical stimuli. These channels can detect and transmit signals generated by mechanical forces, either from the external environment (such as touch or pressure) or from within the cell (such as cell deformation).[33] Upon detecting mechanical stimuli, Piezo channels convert these signals into electrical impulses, relaying to pain receptors within the nervous system and eventually to the brain, enabling the perception of pain.[33] Recent research suggests that Piezo channels are particularly critical in generating and transmitting mechanical pain.[33,40,41] For instance, the Piezo2 channel, expressed in nociceptors involved in osteoarthritis pain, plays a role in mechanical sensitization. Specifically, knocking out the Piezo2 channel in mice protected them from mechanical pain caused by osteoarthritis.[41] Given their crucial role in mechanical pain, Piezo channels are potential targets for treating various painful conditions. Targeting Piezo channels with drugs or treatments could help relieve mechanical pain, from osteoarthritis to neuropathic pain.[42,43]

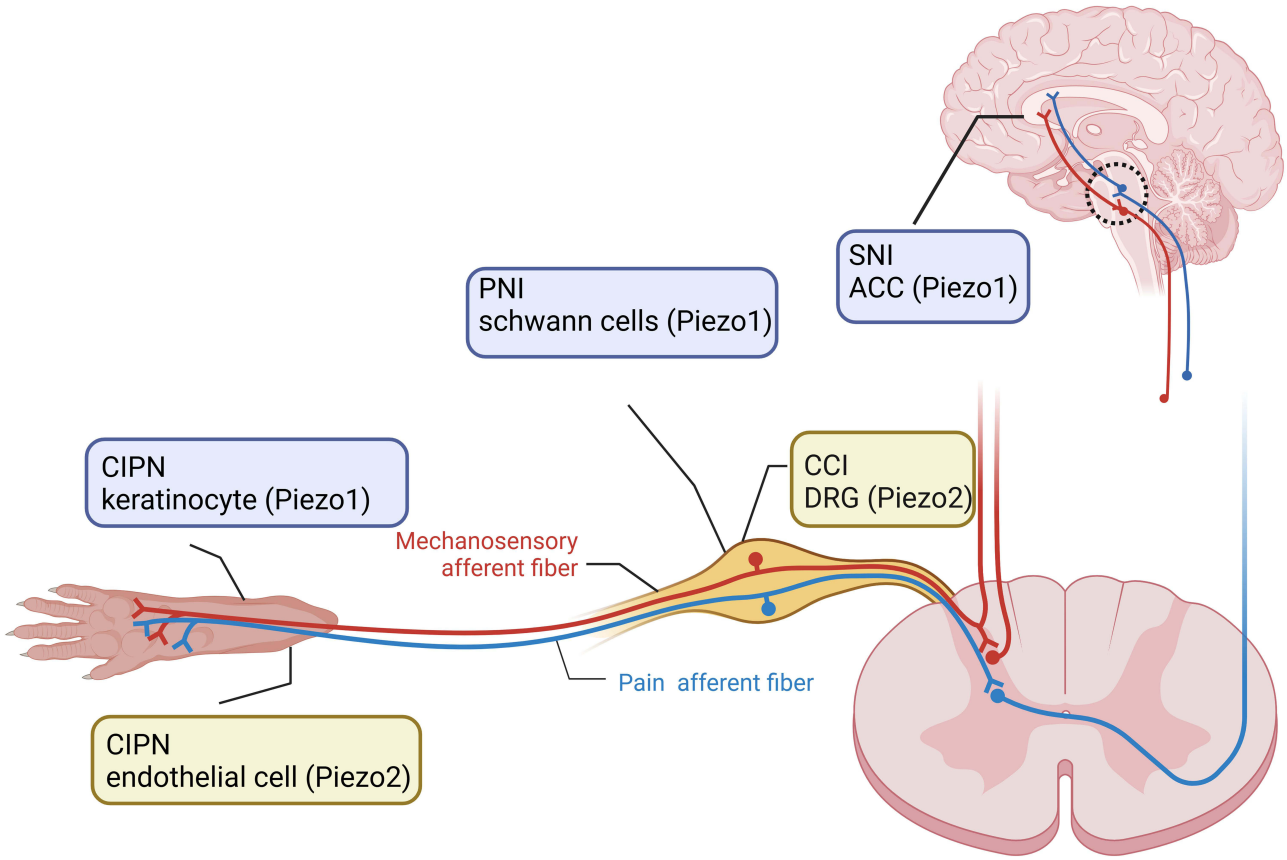

Figure 2 The distribution of Piezo channels in the neuropathic pain pathway. An increasing amount of evidence shows that the Piezo channels acting in different positions participate in the occurrence and development of neuropathic pain. See the text for a detailed description. Created in BioRender. Wan, Y. (2024) https://BioRender.com/c93u267.
Abbreviations: CIPN, Chemotherapy-induced peripheral neuropathy; CCI, Chronic constriction injury; DRG, Dorsal root ganglion; PNI, Peripheral nerve injury; SNI, Spared nerve injury; ACC, Anterior cingulate cortex.

Neuropathic Pain

Neuropathic pain results from injury or disease that impacts the somatosensory nervous system.[44] Chronic neuropathic pain encompasses conditions such as peripheral nerve injury, spinal cord injury, diabetic neuropathy, and neuropathy induced by chemotherapy.[45] Despite numerous studies exploring the pathophysiology process of neuropathic pain, its mechanisms remain unclear (Table 2).

Increasing evidence shows that Piezo channels participate in the development of neuropathic pain. For instance, subcutaneous injection of oligodeoxynucleotides targeting Piezo2 mRNA into rats' hind paws reduced endothelin-1-induced hyperalgesia.[46] Similarly, local infusion of Piezo2 antisense could prevent oxaliplatin-induced mechanical hyperalgesia by impairing endothelial cell function.[46] Additionally, Piezo1 in mouse and human keratinocytes is involved in the mechanical hypersensitivity induced by paclitaxel exposure.[47] These findings suggest that the Piezo proteins act as mechano-transducers in endothelial cells (Piezo2) and keratinocytes (Piezo1), which are required for mechanical hyperalgesia in chemotherapy-induced pain models.

It was reported that Piezo2 is required for light touch and the development of allodynia, and the knockdown of Piezo2 mRNA in mice could enhance thresholds for light touch and allodynia in a chronic constriction injury model.[32] Similarly, the mechanical threshold and response to a brush stroke in $Piezo2^{HoxB8}$ (constitutive Piezo2 knockout anatomically restricted to caudal sensory neurons) mice had no change compared to the reduced mechanical threshold of wildtype mice up to 21 days following spared nerve injury (SNI).[33] In contrast, SNI led to an increase in Piezo1 protein levels specifically in inhibitory parvalbumin (PV)-expressing interneurons within the bilateral anterior cingulate cortex (ACC), while no such increase was observed in glutamatergic CaMKII+ neurons. The NLRP3 inflammasome might be a key

Table 2 Summary of the Role of Piezo Channels in Neuropathic Pain

References	Piezo	Model	Treatment	Effects	Expression
Ferrari et al, 2015[45]	Piezo2	Endothelin-1-induced hyperalgesia and oxaliplatin-induced mechanical hyperalgesia	Subcutaneous plantar injection of Piezo2 antisense in the rat's hind paw	PWT↑	Hind paw endothelial cell
Mikesell et al, 2023[46]	Piezo1	Paclitaxel-induced touch pain	The plantar surface of each hindpaw exposed to amber light (590 nm) 1 min before and during von Frey stimulation	PWT↑	Mouse and human keratinocyte
Eijkelkamp et al, 2013[32]	Piezo2	Unilateral L5 SNT or SNI (CCI) model	Intrathecal Piezo2 antisense injection	PWT↑	DRG sensory neurons
Murthy et al, 2018[33]	Piezo2	Capsaicin-induced inflammation pain and SNI models	$Piezo2^{HoxB8}$ and $Piezo2^{iAdv}$ mice	PWT↑	DRG
Li et al, 2022[39]	Piezo1	SNI	NLRP3 inhibitor MCC950 (10 mg/kg i.p., once a day for 7 days)	PWT↑	Bilateral anterior cingulate cortex (ACC)
Itson-Zoske et al, 2023[47]	Piezo1	PNI Tibial nerve injury (TNI) and common peroneal nerve injury(CPNI)	Selective RNAi silencing of Piezo1 in Schwann cells	PWT↑	Schwann cells
Liu et al, 2021[48]	Piezo2	TN model (chronic constriction injury of the infraorbital nerve)	270 ug/kg GsMTx4 was injected intraperitoneally or IL-6 antibody once daily for 3 consecutive days	PWT↑	Trigeminal ganglion

Abbreviations: PWT, Paw withdrawal threshold; SNT, sciatic nerve transaction; SNL, sciatic nerve ligation; CCI, chronic construction injury; DRG, dorsal root ganglion; i.p., intraperitoneal injection; ↑, upregulation.

factor driving the upregulation of Piezo1 in SNI, contributing to a disrupted balance between excitation and inhibition in the ACC by inducing microglial phagocytosis of PV-INs, thus enhancing spinal pain transmission.[40] These findings indicate that both Piezo1 and Piezo2 are crucial in developing punctate and dynamic allodynia following nerve injury. Additionally, in non-neuronal cells, Piezo1 may act as a mechanotransducer in Schwann cells, playing a role in converting injury-induced mechanical forces into heightened nociceptive sensitivity.[49]

Trigeminal neuralgia (TN) is a prevalent condition affecting the cranial nerves, marked by hyperexcitability often resulting from neurovascular conflict or vascular compression at the cranial nerve root. This pathological process leads to nerve demyelination, where mechanosensitive ion channels, notably Piezo2, may be critically involved. Pulsatile compressions can activate Piezo2 channels, causing a depolarization of the resting potential and inducing a subthreshold oscillatory state of the membrane potential. Under these conditions, minor pressure can readily elevate the membrane potential to its threshold, triggering sodium channel activation and generating action potential in the axon. These ectopic action potentials are perceived as pain when transmitted to the central nervous system.[48] Additional research utilizing a chronic constriction injury model of the infraorbital nerve to investigate trigeminal neuropathic pain revealed a marked upregulation of both Piezo2 and interleukin-6 (IL-6) in TN model rats. Piezo2 expression was detected in C- and A-type neurons, but not in astrocytes. Inhibition of Piezo2 using GsMTx4 significantly impacted dynamic allodynia, pinprick hyperalgesia scores, and mechanical thresholds. These findings indicate that Piezo2 upregulation in pain-afferent neurons following trigeminal nerve injury contributes to neuralgia development, with its expression potentially modulated by inflammatory cytokines such as IL-6.[50]

Diabetic distal symmetric polyneuropathy, the most common type of diabetic peripheral neuropathy, is a debilitating condition often resulting from chronic hyperglycemia. This condition is characterized by increased cutaneous microvessel density, reduced skin blood flow, endothelial dysfunction, and compromised vasodilation, all of which contribute to the clinical manifestations of neuropathy.[51] The dysfunction of microvascular structures in diabetic patients is further complicated by impaired fluid filtration, leading to compromised tissue perfusion. Piezo1 and Piezo2 mechanosensitive ion channels have been identified as significant players in these microvascular disturbances. Recent studies indicate that the expression of Piezo2 in cutaneous mechanoreceptors is altered in both non-painful and painful forms of distal diabetic sensorimotor polyneuropathy, suggesting that Piezo2 may contribute to the onset of neuropathic pain.[52] On the other hand, Piezo1 appears to be crucial for normal vasodilation processes, and a deficiency in this channel is associated with impaired blood vessel relaxation, further exacerbating the microvascular dysfunction observed in diabetic patients.[53] These findings underscore the importance of Piezo channels in the pathophysiology of diabetic neuropathy and highlight their potential as therapeutic targets for managing both pain and vascular complications in affected individuals.

A minority of corneal trigeminal neurons express Piezo2.[54] These channels, located in both the cell bodies and terminals of corneal neurons, play a direct role in acute corneal mechano-nociception. Topical modulation of Piezo2 in

the cornea may offer targeted relief from mechanical irritation and pain in various ocular surface conditions.[55] Dry eye disease is a multifaceted condition with an established pathology, though its complete pathomechanism remains unclear. It is thought to be part of a continuum that includes neuropathic corneal pain. Piezo2 channels at corneal nerve terminals are central to the progression of dry eye disease, which unfolds in three phases: the first phase involves pain-free microinjuries to Piezo2 channels at corneal somatosensory nerve terminals. The second phase is marked by more substantial corneal damage, with C-fiber involvement due to insufficient interaction between Piezo2 and peripheral Piezo1. The third phase involves neuronal sensitization and chronic channelopathy following repeated injuries to Piezo2. These microinjuries to Piezo2 channels at Aδ sensory terminals are critical in dry eye disease and neuropathic corneal pain. The NGF-TrkA signaling pathway in these somatosensory neurons likely drives this microinjury process, with the NGF-TrkA -Piezo2 axis potentially contributing to sex differences observed in dry eye disease.[56]

Visceral Pain

Visceral pain is typically triggered by mechanical distension or stretch, which activates mechanotransductive channels.[57] Mechanosensitive Piezo proteins are crucial in mediating mechanical stimuli that induce visceral pain. Irritable bowel syndrome (IBS), a prevalent functional gastrointestinal disorder, involves Piezo proteins expressed in blood vessel endothelium, which can contribute to endothelial pain sensation.[34] Since intestinal epithelial cells exist in a similarly complex mechanical microenvironment as vascular endothelial cells, Piezo proteins in the intestinal tract are also implicated in mechanically induced visceral pain. Bai et al (2017) were the first to report the expression of Piezo1 and Piezo2 in intestinal epithelial cells in mice, finding a solid correlation between visceral sensitivity and Piezo2 expression in the colon.[34] The selective deletion of stretch-activated Piezo2 channels from TRPV1 lineage neurons led to a significant reduction in mechanically-evoked visceral afferent action potential firing and visceromotor responses to colorectal distension, both under normal conditions and in models of zymosan-induced IBS and partial colon obstruction.[58] As a result, Piezo2 may serve as a biomarker for visceral hypersensitivity in IBS.

A previous study highlighted the essential role of Piezo2 in detecting bladder stretch during filling and maintaining the normal micturition reflex. Knockout of Piezo2 induced a reduced voiding frequency in mice, and the lack of functional Piezo2 showed an insufficient bladder-filling sense in humans.[59] Bladder filling, which mimics mechanical allodynia, is a common trigger for pain associated with interstitial cystitis. Piezo2 channels are present on most bladder primary afferents. In cyclophosphamide (CYP)-induced cystitis, Piezo2 was upregulated in bladder afferent neurons at the mRNA, protein, and functional levels. Knockdown of Piezo2 expression in dorsal root ganglion (DRG) neurons diminished both referred bladder pain and hyperactivity triggered by mechanical stimulation in CYP-treated rats.[60] These findings underscore the role of Piezo channels in visceral mechanical nociception and hypersensitivity.

Musculoskeletal Pain

Chronic musculoskeletal pain is classified according to its central mechanisms, which include persistent inflammation that may be triggered by infectious, autoimmune, or metabolic factors; structural alterations in bones, joints, tendons, or muscles, typical of conditions like symptomatic osteoarthritis; and musculoskeletal pain that occurs secondary to motor nervous system disorders, such as spasticity resulting from spinal cord injuries.[61]

Osteoarthritis (OA) is the most common form of degenerative joint disease, presenting symptoms such as joint pain, tenderness, stiffness, swelling, and deformities.[61] The osteoarticular system is capable of detecting mechanical stress, and the prolonged exposure of articular cartilage to such forces has been closely associated with the onset of OA.[62] Recent research has highlighted the Piezo channel as a critical mediator of mechanical stimulus transduction, with significant expression levels observed in the osteoarticular system.[63,64] Piezo1 proteins mediate the effect of mechanical loading on chondrocytes, driving chondrocyte mechanical injury and contributing to chondrocyte metabolic reaction. This process can be altered by factors influencing membrane prestress, such as cartilage hypo-osmolarity, secondary to proteoglycan loss.[65,66] Intraarticular injection of the spider venom toxin GsMTx4 has been shown to attenuate the injury-inducing effects of mechanical stimulation on chondrocytes.[67–69] One study using an inducible system (the transgenic mouse model AcanCreERT2) to inactivate Piezo1 selectively showed significant attenuation of OA development. Artemisinin, a highly effective antimalarial agent, has been shown to inhibit Piezo1 activation in chondrocytes, thereby alleviating

osteoarthritis (OA) damage in adult mice.[42] Conversely, intra-articular administration of the Piezo1 agonist Yoda1 exacerbates OA-related pathologies induced by surgical intervention.[42] Piezo1 also mediates mechanical stress stimulation in chondrocytes, inducing intracellular Ca^{2+} accumulation, and is associated with chondrocyte apoptosis.[70] Activation of Piezo1 by mechanical loading leads to increased membrane currents, activation of voltage-gated calcium channels, mitochondrial dysfunction, and chondrocytes apoptosis.[65,67]

The role of Piezo2 in osteoarthritis (OA) remains relatively underexplored. However, it is predominantly expressed in nociceptors and contributes to mechanical sensitization in experimental models of osteoarthritis.[71] Obeidat et al (2023) demonstrated that conditional knockout of Piezo2, specifically in nociceptors, protected mechanical sensitization linked to inflammatory joint pain in female mice and joint pain associated with osteoarthritis in male mice.[41]

The following studies started to concentrate on the role of Piezo2 in the development of osteoarthritis and explore the different roles of Piezo1 and Piezo2 in OA. A study using Gdf5Cre transgenic mice to inactivate Piezo1 and Piezo2 found no significant difference in OA progression compared to controls after medial meniscus destabilization.[72] Further research demonstrated that Piezo1, unlike Piezo2, is crucial for chondrocytes function. While Piezo1 deficiency moderately impacts skeletal growth, it severely disrupts postnatal trabecular bone formation. The presence of Piezo1 in chondrocytes is critical for endochondral ossification and the pathological processes associated with OA progression and osteophyte development.[73] Furthermore, genome-wide expression profiling of a chondrogenic cell line identified Ccn2 as a gene specifically regulated by Piezo1 and implicated in OA progression. Clinical data have shown increased expression of both Piezo1 and Ccn2 in the articular cartilage, subchondral bone, and osteophytes of OA patients.[73]

Osteoarthritis (OA) involves mechanical stress and triggers a significant inflammatory response. This inflammatory reaction markedly enhances the Piezo channel currents induced by mechanical stimulation in OA. Significantly, knee OA does not alter the mRNA expression levels of Piezo1 or Piezo2, suggesting increased channel activity occurs without corresponding mRNA expression.[74] Furthermore, inflammatory signaling mediated by IL-1α in articular chondrocytes has been shown to elevate both the expression and function of Piezo1, leading to heightened sensitivity to mechanical stress.[65] Many autoimmune diseases are characterized by pain.[74] In the case of multiple sclerosis, activation of the Piezo1 channel in axons negatively impacts central nervous system myelination.[12] Interestingly, depleting Piezo1 in T cells selectively promotes regulatory T cell proliferation, reducing the severity of experimental autoimmune encephalomyelitis, while having no impact on, lymph node homing, thymic development, or T-cell receptor priming, proliferation, and differentiation.[75]

Studies in this field indicated that Piezo1 in chondrocyte is associated with chondrocyte injury, chondrocyte metabolic reaction, and chondrocyte apoptosis, promoting the development of osteoarthritis. Piezo2, primarily expressed in nociceptors, mediates mechanical hyperalgesia. The synergistic effect of Piezo1 and Piezo2 increased sensitivity to mechanical stimuli and chondrocyte injury, contributing to osteoarthritis development, and mechanical hyperalgesia.

Headache and Orofacial Pain

The headache phase of a migraine is characterized by a pulsating or throbbing sensation, a defining symptom of migraine pain.[14] This pain is closely associated with mechanical hypersensitivity, indicating an enhanced ability to detect mechanical stimuli. Both Piezo1 and Piezo2 channels are present in trigeminal sensory neurons,[76] which innervate the head and face tissues, playing a pivotal role in migraine pain generation. Repetitive nociceptive signaling in trigeminal neurons likely contributes to the mechanical hypersensitivity and allodynia commonly observed in migraines. Mechanical hypersensitivity is directly related to the activation of Piezo channels in peripheral neurons, while allodynia arises from excessive activation of Piezo channels in primary afferents.[14]

Trigeminal neurons, surrounded by pulsating blood vessels, initiate the nociceptive cascade by activating Piezo1 mechanosensitive channels. Satellite glial cells (SGCs) surrounding these neurons also express functional Piezo1 receptors.[77] SGCs are involved in chronic pain by communicating with neurons and modulating their activity, thereby promoting neuroinflammation.[78] Mechanosensitive pathways from neurons to glial cells are pivotal in migraine sensitization, reacting to mechanical stimuli (or Piezo1-specific chemicals) through a calcium-dependent mechanism.[77] In one study, the activity of Piezo1 channels was compared between mouse trigeminal ganglia (TG) neurons and dorsal root ganglia (DRG) neurons using both live calcium imaging and microfluidic chip-based techniques. Results showed that TG

neurons exhibited higher Piezo1 gene expression but were less responsive to the Piezo1 agonist Yoda1 than DRG neurons, supporting the role of Piezo channels in migraine pain mechanisms.[79]

Low-threshold mechanoreceptors are essential in dental pain, as even minor mechanical stimuli can trigger intense tooth pain.[11] Among these mechanoreceptors, Piezo2 channels are recognized for their role in sensory dorsal root ganglion (DRG) neurons and Merkel cells as low-threshold detectors.[80,81] The depletion of Piezo2 in these cells significantly diminished rapidly adapting mechanically induced currents, underscoring its vital role as a low-threshold mechanoreceptor.[11] This suggests that Piezo2-positive mechanoreceptors play a significant role in tooth pain.

Piezo2 is predominantly expressed in mature odontoblasts of rodents and is absent in immature cells.[82] A selective Piezo1 blocker antagonized the inward current induced by odontoblasts in TG neurons, and the response of odontoblasts to mechanical stimuli was inhibited by a Piezo1 antagonist.[83] A recent investigation into the expression of mechanosensitive ion channels in pulp tissues from patients with irreversible pulpitis revealed an upregulation of Piezo1 and a downregulation of Piezo2.[84] Positive correlations were observed between Piezo1 and inflammatory markers (such as IL-1β, TNF-α, and IL-6) and between Piezo2 and pain markers (including NPY and TAC1) in inflamed pulp tissues, with Piezo2 showing a stronger correlation with pain intensity. These findings underscore the involvement of Piezo1 and Piezo2 in the inflammatory and pain responses associated with pulpitis.

The mechanisms underlying chronic pain in masticatory muscles remain unclear. However, sensitization of primary nociceptive afferents following muscle injury or inflammation may regulate multiple genes in the trigeminal ganglia, contributing to muscle hyperalgesia. An RNA sequencing study in rat trigeminal ganglia identified Piezo2 as a potential contributor to masseter hyperalgesia following craniofacial muscle injury or inflammation.[85]

Piezo channels, specifically Piezo1 and Piezo2, play significant roles in various pain mechanisms. In migraines, these channels are involved in the mechanical hypersensitivity and allodynia associated with the condition. Piezo2 acts as a low-threshold mechanoreceptor in tooth pain, while Piezo1 is involved in odontoblastic responses to mechanical stimuli. Piezo2 may contribute to hyperalgesia following inflammation or injury in chronic masticatory muscle pain. These findings highlight the critical roles of Piezo channels in pain and suggest potential therapeutic targets for managing pain associated with different conditions.

Inflammatory Pain

Mechanical injury is one of the inducible factors of inflammation. When mechanical stress is applied to cells, it can cause direct damage and induce the secretion of pro-inflammatory factors, resulting in indirect tissue damage.[86] Repeated or sustained destructive mechanical stimulation can lead to inflammatory diseases. However, the mechanism of mechanic-induced inflammation is not fully understood. Previous studies suggest that Piezo channels play a vital role in developing and progressing inflammatory diseases.[87,88] Piezo channels sense changes in local mechanical stress in inflamed tissues and participate in the development of chronic inflammation[89] For example, tensile load can increase calcium influx in myocardial fibrosis by activating Piezo1 in myocardial fibroblasts, thus promoting inflammation, fibroblast proliferation, and myocardial fibrosis[90] In osteoarthritis, Piezo1 is involved in the apoptosis of cartilage cells and inflammation, leading to increased fluid and pressure within the joint.[91]

The role of Piezo channels in inflammatory pain still needs to be fully understood. Inflammatory pain is generally attributed to an inflammatory response to tissue damage. Research has shown that bradykinin and Complete Freund's Adjuvant (CFA)-induced inflammatory mechanical pain were unaffected in Piezo2iAdv mice.[11] However, in an acute inflammation model, intradermal injection of capsaicin led to the activation of Piezo2-mediated mechanical allodynia.[33] Beyond its well-known function in touch and proprioception, Piezo2 may also play a role in sensory processing in the spinal cord, Schwann cells, and skin melanocytes, in addition to large, low-threshold mechanosensitive primary sensory neurons (PSNs).[33] To further explore Piezo2's role in CFA-induced mechanical hyperalgesia, intrathecal administration of Piezo2 antisense oligodeoxynucleotides (ODN) targeting L4–L5 DRG was introduced three days post-CFA injection. This treatment inhibited mechanical hyperalgesia without affecting thermal hyperalgesia. However, administering Piezo2 antisense ODN three days before CFA injection did not influence mechanical hyperalgesia at 24 hours post-injection.[92] Additionally, Epac1-mediated pain is regulated by G protein kinase 2 (GRK2), which inhibits Epac1-to-Rap1 signaling

and the sensitization of mechanocurrents mediated by Piezo2.[92] Therefore, Piezo2 contributes to inflammatory mechanical hyperalgesia.

Thus, Piezo channels play significant roles in various types of pain and inflammatory responses. Mechanic-induced inflammation involves the activation of Piezo channels, leading to the secretion of pro-inflammatory factors and subsequent tissue damage. In inflammatory pain, Piezo2 is implicated explicitly in mechanical hyperalgesia. Understanding how Piezo channels contribute to inflammation and pain can provide insights into potential therapeutic targets for treating these conditions.

Future Perspectives and Conclusion

This review highlights the mechanisms by which Piezo channels are implicated in various forms of chronic pain, including neuropathic, visceral, musculoskeletal, headache, orofacial, and inflammatory pain. Recent research has primarily focused on inhibiting or knocking down Piezo channels to confirm their role in mechanical sensitivity and chronic pain. However, a more comprehensive understanding of the mechanisms underlying the Piezo channel function remains to be explored.

Most studies on chronic pain have concentrated on the involvement of Piezo channels in the peripheral nervous system. This includes neuronal and non-neuronal cells, such as satellite glial cells, Schwann cells, and epidermal Merkel cells, all of which express functional Piezo1 receptors. These receptors contribute to chronic pain by cross-talking with neurons and modulating neuronal activity. Still, the mechanisms of Piezo channels in the central nervous system need to be sufficiently understood.

The methods for studying Piezo are relatively limited, particularly regarding specific inhibitors. In vivo experiments using knockout mice remain essential for understanding their functions. In vitro, studies have primarily used the small molecules Yoda1[93] or Jedi1 as selective Piezo1 agonists. Yoda1 activates Piezo1 in trigeminal neurons, inducing trigeminal nociceptive signaling[76] and triggering calcium influx in small- and medium-sized DRG neurons.[94] However, further studies are needed to investigate the role of Piezo1 using Yoda1 in chronic pain to understand its physiological functions. Notably, these compounds have not been shown to activate Piezo2, likely due to amino acid sequence variations between Piezo1 and Piezo2, though the exact mechanisms behind this selectivity require further investigation. While Jedi1, containing a furan-3-carboxylic acid group, is also capable of activating the Piezo1 channel, its binding affinity is lower than that of Yoda1. The Yoda1-induced Ca^{2+} influx can be inhibited by GsMTx4, which blocks both Piezo1 and Piezo2 by altering the curvature of the surrounding membrane. However, GsMTx4 may also influence other mechanosensitive ion channels. Additionally, transmembrane channel-like protein 7 (TMC7) has been identified as an inhibitor of Piezo2 in primary sensory neurons, acting through direct interaction without influencing Piezo2 expression or membrane localization.[95] Despite these findings, no specific inhibitors for Piezo1 or Piezo2 have been reported, posing a significant challenge for conducting translational studies. The development of such inhibitors is crucial for advancing our understanding of the roles of Piezo1, Piezo2, and other mechanosensitive channels in pain regulation and their potential clinical applications. Furthermore, it remains unclear whether targeting Piezo1 or Piezo2 would be more beneficial, and further research is needed to draw a conclusion.

Numerous studies have investigated the potential health implications of Piezo channels in humans. Whole-exome sequencing of two patients presenting with distinctive neuromuscular and skeletal symptoms uncovered compound-inactivating variants in Piezo2, resulting in selective impairment of discriminative touch perception.[28] Likewise, individuals with loss-of-function mutations in Piezo2 demonstrate significant deficits in sensitization and painful responses to touch after skin inflammation.[27] These observations indicate that Piezo2 plays a vital role in mechanosensation in humans. Patients with inherited Piezo2 mutations lack touch and proprioception responses, though they retain pressure sensitivity comparable to healthy individuals.[96] Further human studies are necessary to elucidate the translational significance of Piezo channels, particularly Piezo2, in relation to chronic pain.

In conclusion, the specific mechanisms and roles of Piezo channels require further and comprehensive investigation. Understanding the detailed mechanisms of Piezo channels in the peripheral and central nervous systems is crucial for developing effective treatments for chronic pain. Future research should focus on identifying specific inhibitors of Piezo channels, studying their roles in various cell types, and exploring their functions in the central nervous system. This will

provide a deeper understanding of how Piezo channels contribute to chronic pain and aid in developing targeted therapies.

Human and Animal Rights

This article does not include any studies involving human or animal subjects conducted by the authors.

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Disclosure

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