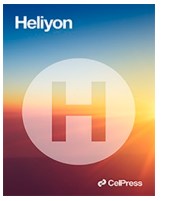
Heliyon 9 (2023) e17989

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Regulation of pain neurotransmitters and chondrocytes metabolism mediated by voltage-gated ion channels: A narrative review

Xinwei Wang, Xueping Li *

Department of Rehabilitation Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing, 210006, China

ARTICLE INFO

Keywords:
Chondrocytes metabolism
Osteoarthritis
Pain
Voltage-gated ion channels

ABSTRACT

Osteoarthritis (OA) is one of the leading causes of chronic pain and dysfunction. It is essential to comprehend the nature of pain and cartilage degeneration and its influencing factors on OA treatment. Voltage-gated ion channels (VGICs) are essential in chondrocytes and extracellular matrix (ECM) metabolism and regulate the pain neurotransmitters between the cartilage and the central nervous system. This narrative review focused primarily on the effects of VGICs regulating pain neurotransmitters and chondrocytes metabolism, and most studies have focused on voltage-sensitive calcium channels (VSCCs), voltage-gated sodium channels (VGSCs), acid-sensing ion channels (ASICs), voltage-gated potassium channels (VGKCs), voltage-gated chloride channels (VGCCs). Various ion channels coordinate to maintain the intracellular environment's homeostasis and jointly regulate metabolic and pain under normal circumstances. In the OA model, the ion channel transport of chondrocytes is abnormal, and calcium influx is increased, which leads to increased neuronal excitability. The changes in ion channels are strongly associated with the OA disease process and individual OA risk factors. Future studies should explore how VGICs affect the metabolism of chondrocytes and their surrounding tissues, which will help clinicians and pharmacists to develop more effective targeted drugs to alleviate the progression of OA disease.

1. Introduction

Osteoarthritis (OA) is a chronic progressive joint disease characterized by articular cartilage degeneration, synovial inflammation, and bone hyperplasia. The clinical manifestations of OA patients are pain, joint stiffness, swelling, and deformation [1]. Currently, the incidence of OA has surpassed 7% worldwide, adversely affecting the quality of life and mental health [2]. The treatment of OA mainly includes pharmacotherapy and physical therapy. According to evidence, non-steroidal anti-inflammatory drugs (NSAIDs) can relieve pain in OA patients, but prolonged NSAIDs usage can cause gastrointestinal, cardiovascular, and renal dysfunction [3]. Glucosamine has a cartilage protection effect but does not relieve pain or improve the motor function of the lower limbs [4–7]. Moreover, NSAIDs and glucosamine fail fundamentally address the nature of cartilage degeneration [8]. Chronic pain caused by OA will gradually lead to hyperalgesia, seriously affecting the life quality of OA patients [9]. Voltage-gated ion channels (VGICs) reportedly relieve pain and regulate chondrocytes metabolism, which is a new topic of interest [10–12]. This narrative review aims to provide some overview regarding the potential of the molecular mechanisms and treatment of VGICs.

* Corresponding author.
E-mail address: lixueping6504@163.com (X. Li).

https://doi.org/10.1016/j.heliyon.2023.e17989
Received 15 January 2023; Received in revised form 15 May 2023; Accepted 4 July 2023
Available online 5 July 2023

2. Literature selection methods

The electronic databases of PubMed were searched through the combination of a series of logic keywords and text words, including "osteoarthritis", "arthritis", "pain", "pain measurement", "chondrocytes metabolism", "cartilage", "voltage-gated ion channels", and "ion channel". The most recent electronic search was conducted in February 2023. The reference lists of retrieved articles and reviews were identified. One researcher (Xinwei W) independently reviewed all the retrieved abstracts and full texts. The eligibility criteria for this review were as follows: (a) The connection between osteoarthritis and voltage-gated ion channels; (b) Osteoarthritis-associated pain and voltage-gated ion channels; (c) Cartilage metabolism and voltage-gated ion channels in osteoarthritis; and (d) Animal or human studies, and in vivo or in vitro studies. The exclusion criteria consisted of the following: (a) The duplicate and similar studies; (b) case reports and the conference abstract; (c) articles not with the osteoarthritis, but the other type of arthritis. The flow diagram is shown in Fig. 1.

2.1. The connection between OA and VGICs

VGICs are vital for all life activities [13] and include sodium, calcium, chloride, and certain types of potassium channels. Pain is associated with imbalances in neurotransmitters, which include inhibitory neurotransmitters and excitatory neurotransmitters [14]. In OA pathology, transport mechanisms of many ion channels of chondrocytes are adversely affected, transmitting nociceptive stimulus signals through A and C fibres to spinal dorsal horn [15]. The glutamate, γ-aminobutyric acid (GABA), or glycine is released spontaneously under physiological conditions. However, excessive excitement of neurons could release more harmful neurotransmitters, which cause hyperalgesia in OA patients [16–19]. Many studies reported that voltage-gated potassium channels (VGKCs) and voltage-gated sodium channels (VGSCs) could regulate the internal rhythmic activity of neurons, thereby affecting the release of neurotransmitters [20–22]. The extracellular matrix (ECM) of chondrocytes is disturbed and releases some inflammation factors to exacerbate cartilage damage when the VGICs of chondrocytes are unbalanced [21]. The effects of various VGICs on regulating pain and chondrocytes metabolism with OA are described in detail in Tables 1 and 2.

2.2. Voltage-sensitive calcium channels (VSCCs)

VSCCs are transmembrane heterotrimeric proteins found in the cell membrane. They are divided into six subtypes, L, T, N, P, Q, and R, based on the conductivity of calcium channels and the voltage sensitivity [23]. VSCCs are located on the cell membrane of all excitable cells, such as neurons, muscle cells, and gland cells, and are mainly responsible for triggering the release of transmitters and regulating cell metabolism [24]. The action potential of neurons depends on N, P, Q, and R types. The N-type channel is regarded as the "neurons" calcium channel, which is one of the main mechanisms of Ca^{2+} to enter the nerve endings of pain receptors and regulate pain-causing nerves [25]. Therefore, the N-type calcium channel is a therapeutic target for OA pain [26]. A previous study reported that the inhibitor of CaV2.2 (the subunit α1β of VSCCs) significantly inhibited ($P < 0.01$) the neuronal responses and reduced pain neurotransmitters in OA rats [27]. Gabapentin and pregabalin are widely used to treat chronic pain, including OA, and the analgesic effect might be related to the binding of the α2δ subunit of VSCCs [28]. Hence, VSCCs blockers may reduce pain-causing neurotransmitters and regulate neuronal excitability, thereby alleviating the pain response of OA.

Some studies have reported that VSCCs contribute to cartilage differentiation and metabolism and play a key role in maintaining the homeostasis of chondrocytes [29]. Intracellular Ca^{2+} is essential for initiating the differentiation process of mesenchymal stem cells into chondrocytes. Mesenchymal stem cells derived from bone marrow can differentiate into muscle cells, adipocytes, chondrocytes, and bone cells. In cartilage differentiation, mesenchymal stem cells express the α2δ1 subunit first. The expression of α1 gradually increases on the third day, inducing cartilage differentiation [30]. Cartilage production would be enhanced in congenital tracheal

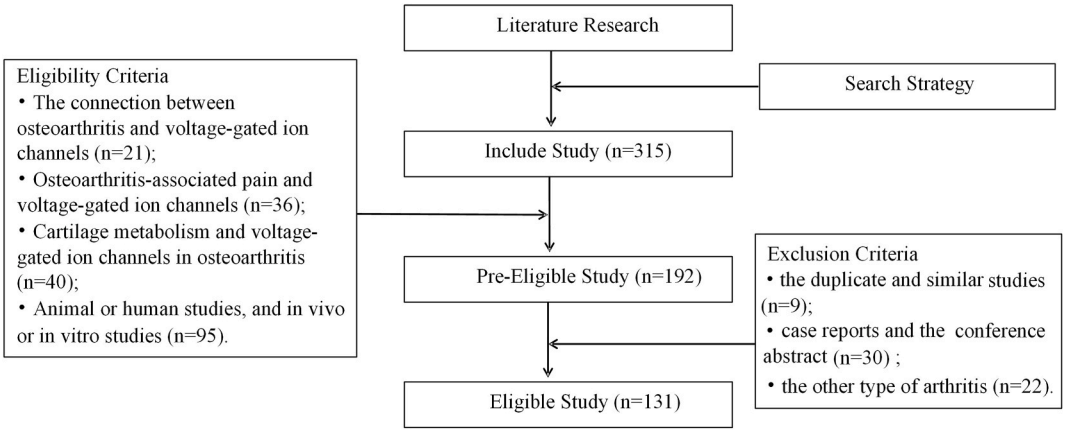


Fig. 1. Flow diagram of literature selection.

Table 1
Effect of VGICs on pain of OA.

VGICs	Subtypes	Mechanisms of pain	Study design
VSCCs	α1	Regulates the release of neurotransmitters	Randomised controlled trials (Gong X et al.)
	α1β	The electrical activity of α1β was enhanced in the OA rats, leading to increased Ca^{2+} influx.	Randomised controlled trials (Rahman W et al.)
	α2δ	α2δ related to neuronal excitability	Randomised controlled trials (El-Awaad E et al.)
	γ	Regulates the biological characteristics of VSCCs	Randomised controlled trials (Klugbauer N et al.)
VGSCs	NaV1.3	High excitability of neurons in the OA rats	Randomised controlled trials (Tao Z et al.)
	NaV1.7	a. Sensory neuron markers critical for pain sensation	Randomised controlled trials (Bufalo M et al.);
	NaV1.8	b. NaV1.7and NaV1.8 expression level increased in the OA rats.	Randomised controlled trials (Ashwell M et al.)
	NaV1.9	c. NaV1.8 inhibitor significantly reduced the firing rate of joint afferents.	Randomised controlled trials (Schuelert N et al.)
ASICs	ASIC3	ASIC3 increased the input signal to the esthesioneure in the OA rats.	Randomised controlled trials (Ikeuchi M et al.)
VGKCs	Kv7	Kv regulate the membrane potential of articular chondrocytes.	Randomised controlled trials (Mobasheri A et al.)
VGCCs	CLC1-2	VGCCs negatively inhibited Ca2+ influx	Randomised controlled trials (Xiao Q et al.)
		Pain neurotransmitters modify ASICs in neurons through opening of VGCCs.	Randomised controlled trials (Chen X et al.)

VGICs: Voltage-gated ion channels. VSCCs: Voltage-sensitive calcium channels. VGSCs: voltage-gated sodium channels. ASICs: Acid-sensing ion channels. VGKCs: voltage-gated potassium channels. VGCCs: voltage-gated chloride channels.

Table 2
Effect of VGICs on chondrocytes metabolism of OA.

VGICs	subtypes	Mechanisms of chondrocytes metabolism	Study design
VSCCs	α2δ1; α1	Participate in cartilage differentiation	Randomised controlled trials (Grajales L et al.)
	α1H	α1H regulates sox9 expression through the calcineurin/NFAT signaling pathway during chondrogenesis.	Randomised controlled trials (Lin S et al.)
VGSCs	α1, β1, β2	expressed in chondrocytes and involved in chondrocytes metabolism.	Randomised controlled trials (Mobasheri A et al.)
	K_V	K_V regulate potential membrane in chondrocytes and mediate electromechanical transduction.	Randomised controlled trials (Shakibaei M et al.)
ASICs	ASIC3	ASIC3 affects cartilage differentiation and metabolism.	Randomised controlled trials (Ikeuchi M et al.)
		ASIC3 could regulate the secretion of hyaluronate.	
	ASIC1α	a. ASIC1α induces the apoptosis of chondrocytes.	Randomised controlled trials (Wu X et al.)
		b. ASIC1a promote inflammation, synovial hyperplasia, articular cartilage and bone destruction.	Narrative review (Xu Y et al.)
		c. Blocking ASICs could protect acid-induced apoptotic injury to chondrocytes.	Randomised controlled trials (Hu W et al.)
		d. Blocking ASICs increased COII and aggrecan mRNA and protein expression in the articular cartilage.	Randomised controlled trials (Yuan F et al.)
VGKCs	BKCa	Regulating neuronal excitability	Randomised controlled trials (Lu R et al.)
VGCCs	CLC1-3	CLC-3 is related to chondrocytes metabolism, leading to achondroplasia.	Randomised controlled trials (Cheng G et al.)
	CLC1-7	CLC-7 mutations lead to intracellular organelle acidification, and osteoblast activity is impaired	Non-randomized controlled trial (Zanardi I et al.); Narrative review (Schaller S et al.)

VGICs:Voltage-gated ion channels. VSCCs: Voltage-sensitive calcium channels. VGSCs: voltage-gated sodium channels. ASICs: Acid-sensing ion channels. VGKCs: voltage-gated potassium channels. VGCCs: voltage-gated chloride channels.

stenosis of the mouse when knocked out α1H (CaV3.2), proving that CaV3.2 is vital to cartilage differentiation [31]. The calcium signal pathways regulate cartilage formation, and the α1 subunit of VSCCs plays an essential role in cartilage metabolism [32]. The function of cartilage formation and cell proliferation is almost eliminated when the α1 subunit is inhibited. Furthermore, VSCCs are essential in maintaining cellular calcium homeostasis in cartilage differentiation [33]. According to in-vitro experiments, T-type VSCCs are crucial in inducing OA-related signal pathways, promoting the release of osteoblast-derived factors, and activating inflammatory factors in chondrocytes. When T-type VSCCs are inhibited after the passage, the inflammatory factors in chondrocytes are decreased, leading to reduced catabolism of chondrocytes and ECM [34]. Nimodipine is a selective calcium channel blocker, which could degrade essential genes of cartilage differentiation and damage ECM of chondrocytes, which in turn verified that VSCCs could regulate cartilage differentiation [35].

2.3. VGSCs

VGSCs are widely distributed in the body, participate in triggering cell action potentials, and transmit various transmitters. The subtypes of VGSCs, including NaV1.3, NaV1.7, NaV1.8, and NaV1.9, are closely related to chronic OA pain [36,37]. They regulate the release of pain-causing neurotransmitters and the excitability of neurons, thereby affecting the occurrence and development of pain [38,39]. The sodium channel expressed in peripheral neurons is mainly Nav1.7, and Nav1.7 is more obviously expressed in nociceptive

sensory neurons than non-nociceptive sensory neurons [40,41]. Nav1.7 knockout mice exhibited reduced mechanical and inflammatory pain through failure to initiate peripheral terminal action potentials, failure to transmit action potentials to secondary neurons in the spinal cord, and defective neurotransmitter release [42]. The overactive Nav1.7 potential produces sustained sodium currents, which induce high-frequency firing of nociceptive neurons and aggravate pain [43]. Nav1.7 mutation is one of the reasons for the hyperexcitability of nociceptors, and the main physiological mechanism is to activate the voltage-dependent hyperpolarization of Nav1.7 and increase the discharge during slow depolarization, thereby causing pain sensitization [44].

VGSCs are essential regulator of chondrocyte proliferation and differentiation. The ion pump and chondrocyte mechanoreceptor complex can induce the rapid homeostasis response to ion disturbance and effectively regulate the intracellular environment and chondrocyte function [45]. Various subtypes of VGSCs are expressed in human chondrocytes, primarily α1, β1, and β2 subtypes [46]. When the chondrocytes are treated with VGSCs blocker lidocaine, the number and viability of chondrocytes are decreased [47,48]. VGSCs impact the formation of cartilage filaments, affecting the framing and homeostasis of chondrocytes [49]. The interactions between chondrocytes and ECM proteins, such as type II collagen and fibronectin, affect chondrocyte proliferation, phenotypic differentiation, and cartilage morphology. Integrins attached to ECM components act as a molecular conduit for signalling, regulating cellular responses and signalling cascades triggered by VGSCs and participate in the transduction of mechanical stimuli in cartilage [50].

2.4. Acid-sensing ion channels (ASICs)

ASICs are a subdivision of the Degenerin/epithelial Na^+ channels (ENaC/DEG) superfamily, primarily distributed in the spinal dorsal root ganglion (DRG) and peripheral nerves of the spinal cord, and are most sensitive to pH changes [51]. Specifically, ASIC3, which exists in chondrocytes, participates in the manifestation and development of OA and regulates pain response and chondrocyte differentiation and metabolism [52,53]. Some studies reported that peripheral inflammation could up-regulate ASIC3 expression in the DRG, indicating that ASIC3 plays a significant role in pain transmission [54,55]. In the ASIC3 gene knocked out mouse model, the mice had a weakened response to noxious stimuli and reduced pain sensitivity [56]. The intra-articular pH value decreased in the OA model, ASIC3 was further activated on the primary afferent fibres and increased the input signal to the esthesioneure, generating action potentials that release more pain neurotransmitters, thus leading to hyperalgesia [57].

ASICs affects cartilage differentiation and metabolism by regulating sodium hyaluronate (HA) in the joints. HA is the main constituent of the synovial fluid in the joint cavity, which lubricates the joints and reduces tissue friction [58]. The injection of HA into the joint cavity can improve the inflammatory response of the synovial tissue, enhance the viscosity of the synovial fluid and lubrication function, and promote the healing and regeneration of articular cartilage, relieve pain, and increase the mobility of joints [59–63]. Abnormal regulation of HA can lead to bone and cartilage destruction. Recent studies have reported that HA could improve bone-marrow-derived mesenchymal stem cells (BMSC) [64] and repair damaged cartilage [65]. ASIC3, a pH sensor of synovial cells, plays a vital role in regulating HA in the respective tissue [66]. The ASIC3 knockout mouse decreased HA expression and increased inflammatory factors in synovium and cartilage. It indicated that ASIC3 could regulate the secretion of HA and inflammatory factors, affecting the anabolism and catabolism of chondrocytes [67]. In addition, ASIC1α induces the apoptosis of chondrocytes in rats by mediating the acidification of calcineurin [68]. When the ASIC channel was blocked, the viability of chondrocytes increased, and the expression of proteoglycan and type II collagen increased, indicating that blocking ASIC can protect chondrocytes from acid-induced apoptosis [69–71].

2.5. VGKCs

The potassium ion channel has the most subtypes and divides into four categories based on different mechanisms: VGKCs, Ca^{2+}-activated K+ channel (KCa), inward rectifying potassium channels (Kir), and tandem pore (2P) domain. VGKCs play an essential role in the potential membrane regulation of primary OA chondrocytes and mediate electromechanical transduction [72]. Specifically, VGKCs subtypes (Kv7) [73], large-conductance calcium-activated K^+ channel (BKCa), Kir2.1, ATP-sensitive potassium channel (K-ATP), and twik-related spinal cord K^+ (TRESK) are closely associated with OA pain [74–76]. It has been reported that specific activation of the neuronal Kv7 channel in the OA rat; when the Kv7 channel is inhibited, mechanical ectopic pain and heat hyperalgesia can be alleviated, thus relieving pain caused by OA [77]. BKCa channel is an essential regulator of neuronal excitability. The BKCa knockout mice exhibited higher nociceptive behaviour in the inflammatory pain model [78]. Moreover, the BKCa channel can affect pain response by regulating the activation of spinal microglia [79]. Kir2.1 can inhibit the development of hyperalgesia, which may be related to the effective inhibition of neuronal excitability [80]. The Kir2.1 gene reduced the frequency of action potential generation and thus inhibited excessive neural activity [81]. K-ATP channel plays a vital role in regulating membrane excitability and releasing neurotransmitters. The expressions of K-ATP channel subunits, including the sulfonylurea receptor (SUR) gene and inwardly rectifying K channel 6.1 (Kir6.1), were significantly up-regulated ($P < 0.05$) in the rat pain model [82]. TRESK can control the transient receptor potential and resting membrane potential of the DRG. Further, TRESK can relieve mechanical pain and reduce inflammatory response and apoptosis. However, intrathecal injection of TRESK short hairpin RNA (shRNA) lentivirus induced mechanical pain [83,84].

VGKCs are potential cellular biomarker and therapeutic target of OA, mediating mechanical conduction, synthesis, and apoptosis of chondrocytes [85,86]. According to the chondrocyte transcriptome database, genes for the KCa, K-ATP, Kir6.1 and Kir6.2 channels in chondrocytes regulate glucose transport capacity and glutamate abundance, thereby affecting chondrogenic differentiation and metabolism [87–89]. When the Kir2.1 channel is inhibited, cartilage formation is reduced, indicating that the Kir2.1 channel mediates cartilage differentiation [90]. The excessive Ca^{2+} influx activates the BKCa channel in chondrocytes, resulting in the hyperpolarization

of the surface potential of chondrocytes and forming a positive feedback mechanism of Ca^{2+} signal conduction and stimulation-secretion coupling, contributing to cartilage differentiation [91]. Furthermore, potassium ion channel activation can promote ECM synthesis and chondrocyte proliferation. According to ultrastructural analysis, mitochondria and granular endoplasmic reticulum expanded, and cytoplasmic vesicles increased in activated chondrocytes, indicating energy metabolism and ECM synthesis of chondrocytes are dependent on VGKCs [92].

2.6. Voltage-gated chloride channels (VGCCs)

In OA pathology, inflammatory cytokines reduce intra-articular pH; thus, chondrocytes are in an acidic environment. In addition to activating ASICs channels on the cell surface, acid pH can activate VGCCs, indirectly affecting Ca^{2+} influx and regulating the pain pathways. In neurons, Ca^{2+} can activate VGCCs and modulate sensory transduction [93]. However, when Ca^{2+} influx increased excessively, VGCCs negatively inhibited Ca^{2+} influx by regulating the intracellular voltage and maintaining the ion balance in the internal environment [94]. Moreover, VGCCs can regulate ASICs in neurons, affecting the release of neurotransmitters and modulating pain responses [95].

VGCCs play a crucial role in regulating chondrocyte apoptosis [96], and small interfering RNA (siRNA) inhibits chloride channel-3 (CLC-3) in the VGCCs family and reduces expression related to chondrocytes metabolism, leading to achondroplasia [97]. Chloride channel-7 (CLC-7) mutations lead to intracellular organelle acidification, and osteoblast activity is impaired [98–100]. Unfortunately, there is currently a lack of studies on the effect of the VGCCs on OA chondrocytes. Therefore, future studies should explore how VGCCs affect knee chondrocyte metabolism.

2.7. The interaction between pain and chondrocytes metabolism

The pathological basis of OA is related to cartilage degeneration, accompanied by a decrease in the chondrocytes' anabolism and an increase in the chondrocytes' catabolism [101]. Knee peripheral receptors transmit nociceptive signals to the DRG, releasing pain-causing neurotransmitters. Therefore, chondrocytes are in an environment of inflammatory and pain-causing factors for a prolonged time. Further, the catabolic level of chondrocytes and ECM proteins increases while the anabolic level decreases, exacerbating cartilage degeneration. Thus, a vicious cycle of processes formed between pain and chondrocytes metabolism [102].

Moreover, the pain produced by OA is closely related to the degree of cartilage damage, and the worse the capacity of the chondrocytes' metabolism, the stronger the pain response produced by OA [103]. When the pain is suppressed, the activity of chondrocytes is also increased [104]. It may be related to altering the microenvironment in which the chondrocytes are located. Therefore, clinicians should manage OA pain symptoms and pay attention to the issues of cartilage metabolism.

2.8. Coordination of various voltage-gated ion channels

Stromal Interaction Molecule 1 (STIM1) is uniformly distributed in the endoplasmic reticulum of normal chondrocytes. OA pathological stimulation causes STIM1 to accumulate and form particles transferred to the cell membrane, which activates the Ca^{2+}

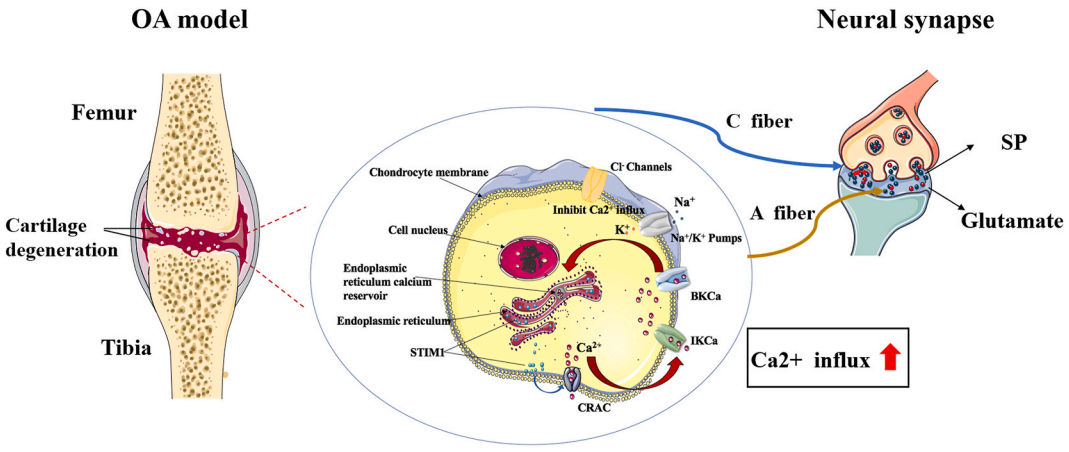


Fig. 2. Mutually coordinated interactions between voltage-gated ion channels in OA chondrocytes. The STIM1 particles in the endoplasmic reticulum were aggregated and transferred to the chondrocyte membrane under the stimulation of inflammatory factors, which activated CRAC channels and extracellular Ca^{2+} influx. Ca^{2+} influx further activated BKCa and IKCa channels, which greatly increased Ca^{2+} influx. A positive feedback loop is formed. The abnormal increase of Ca^{2+} influx in OA chondrocytes leads to the release of nociceptive neurotransmitters (such as substance P and Vglut2) into the synaptic cleft of spinal cord neurons, resulting in a nociceptive response. STIM1: matrix interaction molecule protein 1; CRAC: calcium channel activated by endoplasmic reticulum calcium release; BKCa: large conductance calcium-activated potassium channel; IKCa: medium conductance calcium-activated potassium channel.

release-activated Ca^{2+} channel (CRAC) of the endoplasmic reticulum. Further, Ca^{2+} influx activates BKCa and intermediate Ca^{2+}-Activated K^+ channels (IKCa), increasing Ca^{2+} influx and hyperpolarization of the membrane, and store-operated calcium entry (SOCE) is also promoted. The release of endoplasmic reticulum calcium pool and extracellular Ca^{2+} influx leads to an abnormal increase of Ca^{2+} concentration in OA chondrocytes [105]. Further, the presence of Na^+/K^+ pumps in chondrocytes produces a small net outgoing current that could hyperpolarize the membrane potential of chondrocytes [106,107]. The Cl^- channel depolarises the resting membrane and inhibits Ca^{2+} influx. These ion channels maintain the homeostasis of chondrocytes and synovial fluid and maintain chondrocytes' anabolic and catabolic functions. Regular Ca^{2+} influx causes Ca^{2+} oscillations or intracellular waves contributing to chondrocyte proliferation and maturation [108].

In OA pathology, chondrocytes are exposed to various harmful environments, including inflammation, hypoxia, and mechanical stimulation, which break the balance between various ion channels [109]. Na^+/K^+ pumps and BKCa channels discharge K^+ dysfunction, and Cl^- channel inhibits Ca^{2+} influx. Ion channel imbalance leads to increased Ca^{2+} influx in OA chondrocytes, causing neurons to depolarize and release neurotransmitters into the synaptic space, resulting in hyperalgesia [110,111]. The mechanism is shown in Fig. 2.

2.9. Factors affecting voltage-gated ion channels

The ion channels are the foundation of biological electrical activity, in which opening and closing are affected by the concentration of ions. The ions concentration difference determines the ions flow and maintains the balance of the environment [112]. Ion channels are also susceptible to harmful stimuli (inflammation, virus, temperature, and exercise). Under the influence of inflammatory factors, multiple ion channel signalling pathways are activated [113–115], increasing the neurons' excitability to pain sensitization [116]. When inflammatory factors are suppressed, the ion channel signal changes accordingly, reducing the inflammatory and pain responses. Viruses affect the opening and permeability of various ion channels in cells, and ion channels also play an essential role in the life cycle of viruses. When the virus infects the host cell, the virus expresses some structural proteins, promotes ion transport through the hydrophilic core, regulates the ion homeostasis in the host cell, and creates a favourable environment for the virus to invade the cell or regulate the release of the virus [117]. Some studies have reported that blocking the ion channels of the virus could effectively block the replication and activity of the virus [118,119]. Therefore, viral ion channel proteins are a potential drug target. Temperature can induce the electrical activity patterns of neurons by regulating the rate at which ion channels open and close, thereby influencing the physiological process by which ion channels convert neurotransmitters into electrical signals [120]. Temperature affects the propagation of the action potential of the myelinated axon. Under different temperatures, neuronal action potential propagation depends on the coupling intensity [121]. High temperatures can cause mutations in ion channel proteins, which can cause dysfunction of ion channels [122]. The mechanical load generated by joint movement may be the most critical external factor regulating cartilage metabolism. Mechanical load regulates chondrocyte activity, and pathological overload leads to abnormal ion channel transport and cartilage degeneration and inflammatory infiltration. Exercise can reduce inflammatory and pain responses by regulating ASICs [123]. Moreover, exercise training is sensitive to multiple ion channels such as sodium, potassium, and calcium [124], which can reduce excessive sympathetic excitation and improve the pain sensitization effect, thus helping to improve quality of life and reduce mortality [125–127].

3. Conclusion and prospect

This review summarised the physiological and biochemical mechanisms of various VGICs (VSCCs, VGSCs, ASICs, Kv, and VGCCs), regulating OA pain and chondrocytes metabolism and coordination effects of various channels in chondrocytes, providing ion channel targets for OA treatment. These ion channels play a critical role in chondrocytes and regulate nociceptive neurotransmitters in DRG. However, there were few studies exploring the ion channel targeted drug therapy. With a better understanding of the role of ion channels in chondrocytes, Clinicians and pharmacists can design targeted drugs that improve cartilage destruction, eliminate inflammation, and relieve the pain of patients with OA.

The most of the evidence was based on rat/mouse studies, future studies should focus on human trials. Moreover, future studies also evaluate how different VGICs affect articular and related tissue metabolism of OA disease, including cartilage, subchondral bone, synovium, peripheral blood, inflammatory cell, and pain-causing substances. OA is a chronic disease with multifactorial effects. In addition to pharmacological interventions, further studies should be conducted to explore the effects of non-pharmacological therapies on VGICs in OA, such as physical therapy, traditional Chinese acupuncture therapy, exercise therapy, etc. The non-drug therapy in alleviating pain and delaying cartilage degradation plays an important role [128,129], but the exact mechanism still needs further research. For example, excessive calcium influx can destroy the charge barrier on the surface of chondrocytes, reduce elasticity, and impact the resistance of cartilage [130]. Exercise strengthens the chondrocytes within the calcium influx capacity by enhancing lower limb joints in order to delay the damage of the cartilage [131]. Therefore, comprehensive treatment will be necessary to tackle a complex and slowly progressive disease like OA. It typically involves a combination of medication, exercise, weight management, and lifestyle modifications, which can benefit manage their symptoms and improve their quality of life.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Number: 82072541).

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgements

We thank the National Natural Science Foundation of China (No. 82072541) for financial support. Thanks to Prof. Xueping Li for guidance and contribution of the article. We would like to thank MogoEdit (https://www.mogoedit.com) for its English editing during the preparation of this manuscript.

References

[1] J. Driban, M. Harkey, M. Barbe, R.J. Ward, J.W. MacKay, J.E. Davis, B. Lu, L.L. Price, C.B. Eaton, G.H. Lo, T.E. McAlindon, Risk factors and the natural history of accelerated knee osteoarthritis: a narrative review, BMC Musculoskelet. Disord. 21 (1) (2020) 332.
[2] V.P. Leifer, J.N. Katz, E. Losina, The burden of OA-health services and economics, Osteoarthritis Cartilage 30 (1) (2021) 10–16.
[3] A. Magni, P. Agostoni, C. Bonezzi, G. Massazza, P. Menè, V. Savarino, D. Fornasari, Management of osteoarthritis: expert opinion on NSAIDs, Pain Ther. 10 (2) (2021) 783–808.
[4] P. Alfredo, W. Junior, R. Casarotto, Efficacy of continuous and pulsed therapeutic ultrasound combined with exercises for knee osteoarthritis: a randomized controlled trial, Clin. Rehabil. 34 (4) (2020) 480–490.
[5] J. Dias, L. Cisneros, R. Dias, C. Fritsch, W. Gomes, L. Pereira, M.L. Santos, P.H. Ferreira, Hydrotherapy improves pain and function in older women with knee osteoarthritis: a randomized controlled trial, Braz. J. Phys. Ther. 21 (6) (2017) 449–456.
[6] E. Losina, I. Usiskin, S. Smith, J.K. Sullivan, K.C. Smith, D.J. Hunter, S.P. Messier, A.D. Paltiel, J.N. Katz, Cost-effectiveness of generic celecoxib in knee osteoarthritis for average-risk patients: a model-based evaluation, Osteoarthritis. Cartilage 26 (5) (2018) 641–650.
[7] S. Wang, Y. Wang, L. Huang, Liquid combination of hyaluronan, glucosamine, and chondroitin as a dietary supplement for knee osteoarthritis patients with moderate knee pain: a randomized controlled study, Medicine (Baltim.) 100 (40) (2021), 27405.
[8] J.Y. Reginster, C. Cooper, M. Hochberg, J.P. Pelletier, R. Rizzoli, J. Kanis, E. Abadie, E. Maheu, M.L. Brandi, J.P. Devogelaer, J. Branco, P. D'Hooghe, O. Bruyère, Comments on the discordant recommendations for the use of symptomatic slow-acting drugs in knee osteoarthritis, Curr. Med. Res. Opin. 31 (5) (2015) 1041–1045.
[9] R. Staud, Peripheral and central mechanisms of fatigue in inflammatory and noninflammatory rheumatic diseases, Curr. Rheumatol. Rep. 14 (6) (2012) 539–548.
[10] C. Parisi, V.V. Chandaria, N.C. Nowlan, Blocking mechanosensitive ion channels eliminates the effects of applied mechanical loading on chick joint morphogenesis, Philos. Trans. R. Soc. Lond. B Biol. Sci. 373 (1759) (2018), 20170317.
[11] R. Vaiciuleviciute, D. Bironaite, I. Uzieliene, A. Mobasheri, E. Bernotiene, Cardiovascular drugs and osteoarthritis: effects of targeting ion channels, Cells 10 (10) (2021) 2572.
[12] T. Ning, K. Zhang, B.C. Heng, Z. Ge, Diverse effects of pulsed electrical stimulation on cells - with a focus on chondrocytes and cartilage regeneration, Eur. Cell. Mater. 38 (2019) 79–93.
[13] A. Malfait, R.J. Miller, Emerging targets for the management of osteoarthritis pain, Curr. Osteoporos. Rep. 14 (6) (2016) 260–268.
[14] C. Huang, Y. Lin, D. Lee, C.L. Hsieh, Electroacupuncture relieves CCI-induced neuropathic pain involving excitatory and inhibitory neurotransmitters, Evid.-Based Compl. Alt 2019 (2019), 6784735.
[15] G. Du, W. Chen, L. Li, Q. Zhang, The potential role of mechanosensitive ion channels in substrate stiffness-regulated Ca^{2+} response in chondrocytes, Connect. Tissue Res. 11 (23) (2021) 1–10.
[16] C. Staunton, R. Lewis, R. Barrett-Jolley, Ion channels and osteoarthritic pain: potential for novel analgesics, Curr. Pain Headache Rep. 17 (12) (2013) 378.
[17] K. Zhang, L. Wang, Z. Liu, B. Geng, Y. Teng, X. Liu, Q. Yi, X. Chen, D. Zhao, Y. Xia, Mechanosensory and mechanotransductive processes mediated by ion channels in articular chondrocytes: potential therapeutic targets for osteoarthritis, Channels (Austin, Tex.) 15 (1) (2021) 339–359.
[18] S. Chamberland, A. Evstratova, K. Tóth, Short-term facilitation at a detonator synapse requires the distinct contribution of multiple types of voltage-gated calcium channels, J. Neurosci. 37 (19) (2017) 4913–4927.
[19] L. Xu, C. Liu, L. Chen, G.H. Wu, X.P. Wang, Reduction of SIRT1 mediates monosodium iodoacetate-induced osteoarthritic pain by upregulating p53 expression in rats, Pain Phys. 24 (7) (2021) 1025–1035.
[20] F. Morin, D. Haufler, F. Skinner, J.C. Lacaille, Characterization of voltage-gated K+ currents contributing to subthreshold membrane potential oscillations in hippocampal CA1 interneurons, J. Neurophysiol. 103 (6) (2010) 3472–3489.
[21] E. Thomas, C. Reid, S. Petrou, Mossy fiber sprouting interacts with sodium channel mutations to increase dentate gyrus excitability, Epilepsia 51 (1) (2010) 136–145.
[22] O. Pongs, Regulation of excitability by potassium channels, Results Probl. Cell Differ. 44 (2008) 145–161.
[23] B. Sabatini, K. Svoboda, Analysis of calcium channels in single spines using optical fluctuation analysis, Nature 408 (6812) (2000) 589–593.
[24] N. Garcia, P. Hernández, M. Lanuza, M. Tomàs, V. Cilleros-Mañé, L. Just-Borràs, M. Duran-Vigara, A. Polishchuk, J. Tomàs, Involvement of the voltage-gated calcium channels L- P/Q- and N-types in synapse elimination during neuromuscular junction development, Mol. Neurobiol. 59 (7) (2022) 4044–4064.
[25] A. Calderon-Rivera, K. Gomez, S. Loya-López, R. Khanna, Betulinic acid analogs inhibit N- and T-type voltage-gated calcium channels to attenuate nerve-injury associated neuropathic and formalin models of pain, Neurobiol. Pain 13 (2023), 100116.
[26] J. Heck, A. Palmeira Do Amaral, S. Weißbach, A. El Khallouqi, A. Bikbaev, M. Heine, More than a pore: how voltage-gated calcium channels act on different levels of neuronal communication regulation, Channels (Austin) 15 (1) (2021) 322–338.
[27] W. Rahman, R. Patel, A. Dickenson, Electrophysiological evidence for voltage-gated calcium channel 2 (Cav2) modulation of mechano- and thermosensitive spinal neuronal responses in a rat model of osteoarthritis, Neuroscience 305 (2015) 76–85.
[28] E. El-Awaad, G. Pryymachuk, C. Fried, J. Matthes, J. Isensee, T. Hucho, W.F. Neiss, M. Pietsch, Direct, gabapentin-insensitive interaction of a soluble form of the calcium channel subunit α2δ-1 with thrombospondin-4, Sci. Rep. 9 (1) (2019), 16272.

[29] C. Matta, R. Zákány, A. Mobasheri, Voltage-dependent calcium channels in chondrocytes: roles in health and disease, Curr. Rheumatol. Rep. 17 (7) (2015) 43.
[30] L. Grajales, L.E. Lach, P. Janisch, D.L. Geenen, J. García, Temporal expression of calcium channel subunits in satellite cells and bone marrow mesenchymal cells, Stem Cell Rev. Rep. 11 (3) (2015) 408–422.
[31] S. Lin, B. Tzeng, K. Lee, R.J. Smith, K.P. Campbell, C.C. Chen, Cav3.2 T-type calcium channel is required for the NFAT-dependent Sox9 expression in tracheal cartilage, Proc. Natl. Acad. Sci. U.S.A. 111 (19) (2014) 1990–1998.
[32] Y. Shao, K. Czymmek, P. Jones, V.P. Fomin, K. Akanbi, R.L. Duncan, M.C. Farach-Carson, Dynamic interactions between L-type voltage-sensitive calcium channel Cav1.2 subunits and ahnak in osteoblastic cells, Am. J. Physiol. Cell Physiol. 296 (5) (2009) 1067–1078.
[33] J. Fodor, C. Matta, T. Oláh, T. Juhász, R. Takács, A. Tóth, B. Dienes, L. Csernoch, R. Zákány, Store-operated calcium entry and calcium influx via voltage-operated calcium channels regulate intracellular calcium oscillations in chondrogenic cells, Cell Calcium 54 (1) (2013) 1–16.
[34] P.P. Srinivasan, A. Parajuli, C. Price, L. Wang, R.L. Duncan, C.B. Kirn-Safran, Inhibition of T-type voltage sensitive calcium channel reduces load-induced OA in mice and suppresses the catabolic effect of bone mechanical stress on chondrocytes, PLoS One 10 (5) (2015), 127290.
[35] N. Kaplan, I. Yilmaz, N. Karaarslan, Y.E. Kaya, D.Y. Sirin, H. Ozbek, Does nimodipine, a selective Calcium Channel Blocker, impair chondrocyte proliferation or damage extracellular matrix structures? Curr. Pharmaceut. Biotechnol. 20 (6) (2019) 517–524.
[36] M. Bufalo, M. Almeida, J. Jensen, C. DeOcesano-Pereira, F. Lichtenstein, V.O. Zambelli, Human sensory neuron-like cells and glycated collagen matrix as a model for the screening of analgesic compounds, Cells 11 (2) (2022) 247.
[37] M. Ashwell, M. Freire, A. O'Nan, B.D.X. Lascelles, Characterization of gene expression in naturally occurring feline degenerative joint disease-associated pain, Vet. J. 242 (2019) 42–47.
[38] W. Rahman, A. Dickenson, Osteoarthritis-dependent changes in antinociceptive action of Nav1.7 and Nav1.8 sodium channel blockers: an in vivo electrophysiological study in the rat, Neuroscience 295 (2015) 103–116.
[39] N. Schuelert, J. McDougall, Involvement of Nav 1.8 sodium ion channels in the transduction of mechanical pain in a rodent model of osteoarthritis, Arthritis Res. Ther. 14 (1) (2012) 5.
[40] J. Li, H. Stratton, S. Lorca, P.M. Grace, R. Khanna, Small molecule targeting NaV1.7 via inhibition of the CRMP2-Ubc9 interaction reduces pain in chronic constriction injury (CCI) rats, Channels 16 (1) (2022) 1–8.
[41] G. Goodwin, S. McMurray, E. Stevens, F. Denk, S.B. McMahon, Examination of the contribution of Nav1.7 to axonal propagation in nociceptors, Pain 163 (7) (2022) 869–881.
[42] Y. Huang, L. Zhu, W. Zhang, Q. Tang, Y. Zhong, IL-10 alleviates radicular pain by inhibiting TNF-α/p65 dependent Nav1.7 up-regulation in DRG neurons of rats, Brain Res. 1791 (2022), 147997.
[43] X. Zhou, T. Ma, L. Yang, S. Peng, L. Li, Z. Liu, Spider venom-derived peptide induces hyperalgesia in Nav1.7 knockout mice by activating Nav1.9 channels, Nat. Commun. 11 (1) (2020) 2293.
[44] W. Rahman, A. Dickenson, Osteoarthritis-dependent changes in antinociceptive action of Nav1.7 and Nav1.8 sodium channel blockers: an in vivo electrophysiological study in the rat, Neuroscience 295 (2015) 103–116.
[45] R. Lewis, C. Feetham, L. Gentles, J. Penny, L. Tregilgas, W. Tohami, R. Barrett-Jolley, Benzamil sensitive ion channels contribute to volume regulation in canine chondrocytes, Br. J. Pharmacol. 168 (7) (2013) 1584–1596.
[46] A. Mobasheri, E. Trujillo, M. Arteaga, P. Martín-Vasallo, Na(+), K(+)-ATPase subunit composition in a human chondrocyte cell line; evidence for the presence of α1, α3, β1, β2 and β3 isoforms, Int. J. Mol. Sci. 13 (4) (2012) 5019–5034.
[47] D. Adler, J. Frellesen, C. Karlsen, L.D. Jensen, A.S.Q. Dahm, L.C. Berg, Evaluation of the in vitro effects of local anesthetics on equine chondrocytes and fibroblast-like synoviocytes, Am. J. Vet. Res. 82 (6) (2021) 478–486.
[48] B. Jacob, T. Zippelius, N. Kloss, K. Benad, C. Schwerdt, P. Hoff, G. Matziolis, E. Röhner, Local anesthetics' toxicity toward human cultured chondrocytes: a comparative study between lidocaine, bupivacaine, and ropivacaine, Cartilage 10 (3) (2019) 364–369.
[49] B. Chan, J. Parreno, M. Glogauer, Y. Wang, R. Kandel, Adseverin, an actin binding protein, regulates articular chondrocyte phenotype, J. Tissue Eng. Regen. Med. 13 (8) (2019) 1438–1452.
[50] M. Shakibaei AM, ß1-integrins co-localize with Na, K-ATPase, epithelial sodium channels (ENaC) and voltage activated calcium channels (VACC) in mechanoreceptor complexes of mouse limb-bud chondrocytes, Histol. Histopathol. 18 (2003) 343–351.
[51] S. Dürrnagel, B. Falkenburger, S. Gründer, High Ca(2+) permeability of a peptide-gated DEG/ENaC from Hydra, J. Gen. Physiol. 140 (4) (2012) 391–402.
[52] N. Rotpenpian, T. Arayapisit, A. Roumwong, A. Wanasuntronwong, A standardized extract of Centella asiatica (ECa 233) prevents temporomandibular joint osteoarthritis by modulating the expression of local inflammatory mediators in mice, J. Appl. Oral Sci. 29 (2021), 20210329.
[53] R.P. Zhou, W.L. Ni, B.B. Dai, F.H. Chen, ASIC2a overexpression enhances the protective effect of PcTx1 and APETx2 against acidosis-induced articular chondrocyte apoptosis and cytotoxicity, Gene 642 (2018) 230–240.
[54] W.N. Chen, C.H. Lee, S.H. Lin, C.C. Chen, Roles of ASIC3, TRPV1, and NaV1.8 in the transition from acute to chronic pain in a mouse model of fibromyalgia, Mol. Pain 10 (2014) 40.
[55] M. Izumi, M. Ikeuchi, Q. Ji, T. Tani, Local ASIC3 modulates pain and disease progression in a rat model of osteoarthritis, J. Biomed. Sci. 19 (2012) 77.
[56] C. Chen, A. Zimmer, W. Sun, J. Hall, M.J. Brownstein, A. Zimmer, A role for ASIC3 in the modulation of high-intensity pain stimuli, Proc. Natl. Acad. Sci. U.S.A. 99 (13) (2002) 8992–8997.
[57] M. Ikeuchi, S. Kolker, L. Burnes, R.Y. Walder, K.A. Sluka, Role of ASIC3 in the primary and secondary hyperalgesia produced by joint inflammation in mice, Pain 137 (3) (2008) 662–669.
[58] G. Lee, W. Kwak, K. Lee, Effects and safety of intra-articular sodium hyaluronate injection for the treatment of ankle osteoarthritis: a prospective clinical trial, J. Foot Ankle Surg. 61 (2) (2022) 345–349.
[59] M. Ikeuchi, M. Izumi, K. Aso, N. Sugimura, T. Kato, T. Tani, Effects of intra-articular hyaluronic acid injection on immunohistochemical characterization of joint afferents in a rat model of knee osteoarthritis, Eur. J. Pain 19 (3) (2015) 334–340.
[60] S. Alnasser, F. AlHussain, H. Asiri, A. Almutairi, H. Alsanawi, A.A. Altamimi, Y.A. Asiri, O.A. Almohammed, Y. AlRuthia, Orthopedic surgeons' views of hyaluronic acid formulations in the management of knee osteoarthritis: a questionnaire-based cross-sectional study, Medicina (Kaunas) 57 (9) (2021) 990.
[61] P. Diaz-Rodriguez, C. Mariño, J. Vázquez, J.R. Caeiro-Rey, M. Landin, Targeting joint inflammation for osteoarthritis management through stimulus-sensitive hyaluronic acid based intra-articular hydrogels, Mater Sci. Eng. C Mater. Biol. Appl 128 (2021), 112254.
[62] M. Monteiro Do Nascimento, F. Ambrosio, D. Ferraraz, H. Windisch-Neto, D.R. De Araujo, Sulforaphane-loaded hyaluronic acid-poloxamer hybrid hydrogel enhances cartilage protection in osteoarthritis models, Mater. Sci. Eng. C Mater. Biol. Appl. 128 (2021), 112345.
[63] M. Chang, P. Chiang, Y. Kuo, C.L. Peng, K.Y. Chen, Y.C. Chiang, Hyaluronan-loaded liposomal dexamethasone-diclofenac nanoparticles for local osteoarthritis treatment, Int. J. Mol. Sci. 22 (2) (2021) 665.
[64] G. Monaco, A. El Haj, M. Alini, M.J. Stoddart, Sodium hyaluronate supplemented culture medium combined with joint-simulating mechanical loading improves chondrogenic differentiation of human mesenchymal stem cells, Eur. Cell. Mater. 41 (2021) 616–632.
[65] Ö. Karabıyık Acar, S. Bedir, A. Kayitmazer, G.T. Kose, Chondro-inductive hyaluronic acid/chitosan coacervate-based scaffolds for cartilage tissue engineering, Int. J. Biol. Macromol. 188 (2021) 300–312.
[66] M. Niibori, Y. Kudo, T. Hayakawa, K. Ikoma-Seki, R. Kawamata, A. Sato, K. Mizumura, Mechanism of aspirin-induced inhibition on the secondary hyperalgesia in osteoarthritis model rats, Heliyon 6 (5) (2020) 3963.
[67] S. Kolker, R. Walder, Y. Usachev, J. Hillman, D.L. Boyle, G.S. Firestein, K.A. Sluka, Acid-sensing ion channel 3 expressed in type B synoviocytes and chondrocytes modulates hyaluronan expression and release, Ann. Rheum. Dis. 69 (5) (2010) 903–909.
[68] X. Wu, G. Ren, R. Zhou, J. Ge, F.H. Chen, The role of Ca^{2+} in acid-sensing ion channel 1a-mediated chondrocyte pyroptosis in rat adjuvant arthritis, Lab. Invest. 99 (4) (2019) 499–513.
[69] W. Hu, F. Chen, F. Yuan, T.Y. Zhang, F.R. Wu, M.Y. Lin, Blockade of acid-sensing ion channels protects articular chondrocytes from acid-induced apoptotic injury, Inflamm. Res. 61 (4) (2012) 327–335.

[70] F. Yuan, F. Chen, W. Lu, X. Li, J.P. Li, C.W. Li, R.S. Xu, F.R. Wu, W. Hu, T.Y. Zhang, Inhibition of acid-sensing ion channels in articular chondrocytes by amiloride attenuates articular cartilage destruction in rats with adjuvant arthritis, Inflamm. Res. 59 (11) (2010) 939–947.
[71] Y. Xu, F. Chen, Acid-sensing ion channel-1a in articular chondrocytes and synovial fibroblasts: a novel therapeutic target for rheumatoid arthritis, Front. Immunol. 11 (2020), 580936.
[72] A. Mobasheri, T. Gent, M. Womack, S.D. Carter, P.D. Clegg, R. Barrett-Jolley, Quantitative analysis of voltage-gated potassium currents from primary equine (Equus caballus) and elephant (Loxodonta africana) articular chondrocytes, Am. J. Physiol. Regul. Integr. Comp. Physiol. 289 (1) (2005) 172–180.
[73] X. Zhang, H. Zhang, N. Zhou, J. Xu, M. Si, Z. Jia, X. Du, H. Zhang, Tannic acid modulates excitability of sensory neurons and nociceptive behavior and the Ionic mechanism, Eur. J. Pharmacol. 764 (2015) 633–642.
[74] C. Pui Ping, M.N. Akhtar, D.A. Israf, E.K. Perimal, M.R. Sulaiman, Possible participation of ionotropic glutamate receptors and l-arginine-nitric oxide-cyclic guanosine monophosphate-ATP-sensitive K^+ channel pathway in the antinociceptive activity of cardamonin in acute pain animal models, Molecules 25 (22) (2020) 5385.
[75] J. Zhou, H. Chen, C. Yang, J. Zhong, W. He, Q. Xiong, Reversal of TRESK downregulation alleviates neuropathic pain by inhibiting activation of gliocytes in the spinal cord, Neurochem. Res. 42 (5) (2017) 1288–1298.
[76] I.M. Hdud, A. Mobasheri, P.T. Loughna, Effect of osmotic stress on the expression of TRPV4 and BKCa channels and possible interaction with ERK1/2 and p38 in cultured equine chondrocytes, Am. J. Physiol. Cell Physiol. 306 (11) (2014) 1050–1057.
[77] H. Li, F. Wang, X. Wang, R. Sun, J. Chen, B. Chen, Y. Zhang, Antinociceptive efficacy of retigabine in the monosodium lodoacetate rat model for osteoarthritis pain, Pharmacology 95 (5–6) (2015) 251–257.
[78] R. Lu, R. Lukowski, M. Sausbier, D.D. Zhang, M. Sisignano, C.D. Schuh, R. Kuner, P. Ruth, G. Geisslinger, A. Schmidtko, BKCa channels expressed in sensory neurons modulate inflammatory pain in mice, Pain 155 (3) (2014) 556–565.
[79] K. Imari, Y. Harada, J. Zhang, Y. Mori, Y. Hayashi, KCNMB3 in spinal microglia contributes to the generation and maintenance of neuropathic pain in mice, Int. J. Mol. Med. 44 (4) (2019) 1585–1593.
[80] C. Ma, J. Rosenzweig, P. Zhang, D.C. Johns, R.H. LaMotte, Expression of inwardly rectifying potassium channels by an inducible adenoviral vector reduced the neuronal hyperexcitability and hyperalgesia produced by chronic compression of the spinal ganglion, Mol. Pain 6 (2010) 65.
[81] N. Boulis, C. Handy, C. Krudy, E.M. Donnelly, T. Federici, C.K. Franz, E.M. Barrow, Q. Teng, P. Kumar, D. Cress, Regulated neuronal neuromodulation via spinal cord expression of the gene for the inwardly rectifying potassium channel 2.1 (Kir2.1), Neurosurgery 72 (4) (2013) 653–661.
[82] X. Wu, W. Liu, Y. Liu, Z.J. Huang, Y.K. Zhang, X.J. Song, Reopening of ATP-sensitive potassium channels reduces neuropathic pain and regulates astroglial gap junctions in the rat spinal cord, Pain 152 (11) (2011) 2605–2615.
[83] M. Lengyel, D. Hajdu, A. Dobolyi, J. Rosta, G. Czirják, M. Dux, P. Enyedi, TRESK background potassium channel modifies the TRPV1-mediated nociceptor excitability in sensory neurons, Cephalalgia 41 (7) (2021) 827–838.
[84] J. Zhou, W. Lin, H. Chen, Y. Fan, C. Yang, TRESK contributes to pain threshold changes by mediating apoptosis via MAPK pathway in the spinal cord, Neuroscience 339 (2016) 622–633.
[85] A. Mobasheri, R. Lewis, A. Ferreira-Mendes, A. Rufino, C. Dart, R. Barrett-Jolley, Potassium channels in articular chondrocytes, Channels (Austin) 6 (6) (2012) 416–425.
[86] A. Mobasheri, T.C. Gent, M.D. Womack, S.D. Carter, P.D. Clegg, R. Barrett-Jolley, Quantitative analysis of voltage-gated potassium currents from primary equine (Equus caballus) and elephant (Loxodonta africana) articular chondrocytes, Am. J. Physiol.-Reg. I 289 (1) (2005) 172–180.
[87] A. Rufino, S. Rosa, F. Judas, A. Mobasheri, M.C. Lopes, A.F. Mendes, Expression and function of K(ATP) channels in normal and osteoarthritic human chondrocytes: possible role in glucose sensing, J. Cell. Biochem. 114 (8) (2013) 1879–1889.
[88] C. Matta, R. Lewis, C. Fellows, G. Diszhazi, J. Almassy, N. Miosge, J. Dixon, M.C. Uribe, S. May, S. Poliska, R. Barrett-Jolley, J. Fodor, P. Szentesi, T. Hajdú, A. Keller-Pinter, E. Henslee, F.H. Labeed, M.P. Hughes, A. Mobasheri, Transcriptome-based screening of ion channels and transporters in a migratory chondroprogenitor cell line isolated from late-stage osteoarthritic cartilage, J. Cell. Physiol. 236 (11) (2021) 7421–7439.
[89] R. Barrett-Jolley, R. Lewis, R. Fallman, A. Mobasheri, The emerging chondrocyte channelome, Front. Physiol. 14 (1) (2010) 135.
[90] J. Pini, S. Giuliano, J. Matonti, L. Gannoun, D. Simkin, M. Rouleau, S. Bendahhou, Osteogenic and chondrogenic master genes expression is dependent on the Kir2.1 potassium channel through the bone morphogenetic protein pathway, J. Bone Miner. Res. 33 (10) (2018) 1826–1841.
[91] Y. Suzuki, S. Ohya, H. Yamamura, W.R. Giles, Y. Imaizumi, A new splice variant of large conductance Ca^{2+}-activated K^+ (BK) channel α subunit alters human chondrocyte function, J. Biol. Chem. 291 (46) (2016) 24247–24260.
[92] X. Li, C. Liu, W. Liang, H. Ye, W. Chen, R. Lin, Z. Li, X. Liu, M. Wu, Millimeter wave promotes the synthesis of extracellular matrix and the proliferation of chondrocyte by regulating the voltage-gated K^+ channel, J. Bone Miner. Metabol. 32 (4) (2014) 367–377.
[93] C. Mura, R. Delgado, M. Delgado, D. Restrepo, J. Bacigalupo, A CLCA regulatory protein present in the chemosensory cilia of olfactory sensory neurons induces a Ca^{2+}-activated Cl^- current when transfected into HEK293, BMC Neurosci. 18 (1) (2017) 61.
[94] Q. Xiao, K. Yu, P. Perez-Cornejo, Y. Cui, J. Arreola, H.C. Hartzell, Voltage- and calcium-dependent gating of TMEM16A/Ano1 chloride channels are physically coupled by the first intracellular loop, Proc. Natl. Acad. Sci. U.S.A. 108 (21) (2011) 8891–8896.
[95] X. Chen, P. Whissell, B. Orser, J.F. MacDonald, Functional modifications of acid-sensing ion channels by ligand-gated chloride channels, PLoS One 6 (7) (2011), e21970.
[96] M. Tian, Y. Duan, X. Duan, Chloride channels regulate chondrogenesis in chicken mandibular mesenchymal cells, Arch. Oral Biol. 55 (12) (2010) 938–945.
[97] G. Cheng, Z. Shao, B. Chaudhari, D.K. Agrawal, Involvement of chloride channels in TGF-beta1-induced apoptosis of human bronchial epithelial cells, Am. J. Physiol. Lung Cell Mol. Physiol. 293 (5) (2007) 1339–1347.
[98] K. Henriksen, C. Thudium, C. Christiansen, M.A. Karsdal, Novel targets for the prevention of osteoporosis - lessons learned from studies of metabolic bone disorders, Expert Opin. Ther. Targets 19 (11) (2015) 1575–1584.
[99] I. Zanardi, G. Zifarelli, M. Pusch, An optical assay of the transport activity of ClC-7, Sci. Rep. 3 (2013) 1231.
[100] S. Schaller, K. Henriksen, M. Sørensen, M.A. Karsdal, The role of chloride channels in osteoclasts: ClC-7 as a target for osteoporosis treatment, Drug News Perspect. 18 (8) (2005) 489–495.
[101] N. Yoshioka, G. Young, D. Khajuria, F. Kamal, Structural changes in the collagen network of joint tissues in late stages of murine OA, Sci. Rep. 12 (1) (2022) 9159.
[102] Y. Tani, M. Sato, M. Maehara, J. Mochida, The effects of using vitrified chondrocyte sheets on pain alleviation and articular cartilage repair, J. Tissue Eng. Regen. Med. 11 (12) (2017) 3437–3444.
[103] L. Nwosu, P. Mapp, V. Chapman, D.A. Walsh, Relationship between structural pathology and pain behaviour in a model of osteoarthritis (OA), Osteoarthritis. Cartilage 24 (11) (2016) 1910–1917.
[104] J. Dragoo, T. Korotkova, R. Kanwar, B. Wood, The effect of local anesthetics administered via pain pump on chondrocyte viability, Am. J. Sports Med. 36 (8) (2008) 1484–1488.
[105] J. Fodor, C. Matta, T. Oláh, R. Zákány, Store-operated calcium entry and calcium influx via voltage-operated calcium channels regulate intracellular calcium oscillations in chondrogenic cells, Cell Calcium 54 (1) (2013) 1–16.
[106] M. Maleckar, P. Martín-Vasallo, W. Giles, A. Mobasheri, Physiological effects of the electrogenic current generated by the Na+/K+ pump in mammalian articular chondrocytes, Bioelectricity 2 (3) (2020) 258–268.
[107] M. Shakibaei, A. Mobasheri, Beta1-integrins co-localize with Na, K-ATPase, epithelial sodium channels (ENaC) and voltage activated calcium channels (VACC) in mechanoreceptor complexes of mouse limb-bud chondrocytes, Histol. Histopathol. 18 (2) (2003) 343–351.
[108] R. McDonough, R. Gilbert, J. Gleghorn, C. Price, Targeted Gq-GPCR activation drives ER-dependent calcium oscillations in chondrocytes, Cell Calcium 94 (2021), 102363.
[109] W. Gao, H. Hasan, D. Anderson, W. Lee, The role of mechanically-activated ion channels Piezo1, Piezo2, and TRPV4 in chondrocyte mechanotransduction and mechano-therapeutics for osteoarthritis, Front. Cell Dev. Biol. 10 (2022), 885224.

[110] S. Pitake, L.J. Middleton, I. Abdus-Saboor, S.K. Mishra, Inflammation induced sensory nerve growth and pain hypersensitivity requires the N-type calcium channel Cav2.2, Front. Neurosci. 13 (2019).
[111] I. Uzieliene, D. Bironaite, R. Miksiunas, E. Bernotiene, R. Vaiciuleviciute, A. Mobasheri, The effect of CaV1.2 inhibitor nifedipine on chondrogenic differentiation of human bone marrow or menstrual blood-derived mesenchymal stem cells and chondrocytes, Int. J. Mol. Sci. 24 (7) (2023) 6730.
[112] U. Kachroo, A. Livingston, E. Vinod, S. Sathishkumar, P.R.J.V.C. Boopalan, Comparison of electrophysiological properties and gene expression between human chondrocytes and chondroprogenitors derived from normal and osteoarthritic cartilage, Cartilage 11 (3) (2020) 374–384.
[113] W. Bai, M. Liu, Q. Xiao, The diverse roles of TMEM16A Ca2+-activated Cl- channels in inflammation, J. Adv. Res. 33 (2021) 53–68.
[114] K. Sluka, N. Gregory, The dichotomized role for acid sensing ion channels in musculoskeletal pain and inflammation, Neuropharmacology 94 (2015) 58–63.
[115] S. Partida-Sanchez, B. Desai, A. Schwab, S. Zierler, Editorial: TRP channels in inflammation and immunity, Front. Immunol. 12 (2021), 684172.
[116] D. Duzhyy, N. Voitenko, P. Belan, Peripheral inflammation results in increased excitability of capsaicin-insensitive nociceptive DRG neurons mediated by upregulation of ASICs and voltage-gated ion channels, Front. Cell. Neurosci. 15 (2021), 723295.
[117] S. Gargan, N. Stevenson, Unravelling the immunomodulatory effects of viral ion channels, towards the treatment of disease, Viruses 13 (11) (2021).
[118] A. Premkumar, C. Horan, P. Gage, Dengue virus M protein C-terminal peptide (DVM-C) forms ion channels, J. Membr. Biol. 204 (1) (2005) 33–38.
[119] A. Premkumar, L. Wilson, G. Ewart, P.W. Gage, Cation-selective ion channels formed by p7 of hepatitis C virus are blocked by hexamethylene amiloride, FEBS Lett. 557 (1–3) (2004) 99–103.
[120] Y. Xu, J. Ma, X. Zhan, Y. Jia, Temperature effect on memristive ion channels, Cogn. Neurodyn. 13 (6) (2019) 601–611.
[121] Q. Ding, Y. Jia, Effects of temperature and ion channel blocks on propagation of action potential in myelinated axons, Chaos 31 (5) (2021), 53102.
[122] C. Egri, P. Ruben, A hot topic: temperature sensitive sodium channelopathies, Channels (Austin) 6 (2) (2012) 75–85.
[123] T. Khataei, A. Harding, M. Janahmadi, M. El-Geneidy, H. Agha-Alinejad, H. Rajabi, P.M. Snyder, K.A. Sluka, C.J. Benson, ASICs are required for immediate exercise-induced muscle pain and are downregulated in sensory neurons by exercise training, J. Appl. Physiol. 129 (1) (2020) 17–26.
[124] A. Mobasheri, C. Matta, I. Uzielienè, E. Bernotiene, The chondrocyte channelome: a narrative review, Joint Bone Spine 86 (1) (2019) 29–35.
[125] J. Hong, S. Fu, L. Gao, H.J. Wang, Voltage-gated potassium channel dysfunction in dorsal root ganglia contributes to the exaggerated exercise pressor reflex in rats with chronic heart failure, Am. J. Physiol. Heart Circ. Physiol. 321 (2) (2021) 461–474.
[126] M. Hostrup, J. Bangsbo, Limitations in intense exercise performance of athletes - effect of speed endurance training on ion handling and fatigue development, J. Physiol. 595 (9) (2017) 2897–2913.
[127] R. Floyd, S. Wray, P. Martín-Vasallo, A. Mobasheri, Differential cellular expression of FXYD1 (phospholemman) and FXYD2 (gamma subunit of Na, K-ATPase) in normal human tissues: a study using high density human tissue microarrays, Ann. Anat. 192 (1) (2010) 7–16.
[128] C.Y. Zeng, Z.R. Zhang, Z.M. Tang, F.Z. Hua, Benefits and mechanisms of exercise training for knee osteoarthritis, Front. Physiol. 12 (2021), 794062.
[129] C.J. Lee, W.T. Luo, K.W. Tam, T.W. Huang, Comparison of the effects of acupotomy and acupuncture on knee osteoarthritis: a systematic review and meta-analysis, Complement. Ther. Clin. 50 (2023), 101712.
[130] Y. Wei, D. Zheng, X. Guo, L. Bai, Transient receptor potential channel, Vanilloid 5, induces chondrocyte apoptosis in a rat osteoarthritis model through the mediation of Ca^{2+} influx, Cell. Physiol. Biochem. 46 (2) (2018) 687–698.
[131] Z. Li, Z. Huang, H. Zhang, L. Bai, IRE1-mTOR-PERK Axis coordinates autophagy and ER stress-apoptosis induced by P2X7-mediated Ca2+ influx in osteoarthritis, Front. Cell Dev. Biol. 9 (2021), 695041.