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REVIEW

Targeting the TRPV1 pain pathway in osteoarthritis of the knee

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ABSTRACT

Introduction: The growing prevalence and lack of effective pain therapies for knee osteoarthritis (KOA) results in a substantial unmet need for novel analgesic therapies. The transient receptor potential vanilloid 1 (TRPV1) receptor is expressed in subsets of nociceptive sensory neurons and has major roles in pain transmission and regulation. In the structures of the knee joint, nociceptors are present in abundance.

Areas covered: TRPV1-expressing nociceptors in the knee represent a rational target to modulate activity at the origin of the pain pathway in KOA and may avoid systemic side effects seen with currently available analgesics. TRPV1 antagonists can induce analgesia, but hyperthermia and thermal hypesthesia side effects have limited their utility. Clinical development of TRPV1 agonists for pain management has progressed further than that of TRPV1 antagonists. Capsaicin and resiniferatoxin have provided proof-of-concept for the modulation of TRPV1 activity in KOA.

Expert opinion: Intra-articular administration of TRPV1 agonists enables direct delivery to target nerve terminals in the knee, offering a potentially transformative approach for the management of pain associated with KOA. Here, we explore the advances in understanding innervation of the knee joint in KOA, the role of TRPV1-expressing neurons and progress in developing TRPV1 modulators for KOA.

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innervation; intra-articular; nociceptor; osteoarthritis; pain; resiniferatoxin; transient receptor potential vanilloid 1; TRPV1 agonist

1. Introduction

Osteoarthritis (OA) is a major cause of chronic pain and functional disability [1]. The knee is the most common site of OA, with a 2020 global age-standardized prevalence of 4307.4 cases per 100,000, and it is estimated that by 2050 the prevalence will have grown by 74.9%, with 642 million individuals having knee OA (KOA) worldwide [2].

While previously thought of as a passive degenerative disease resulting from accumulated wear and tear, OA is now known to involve an active dynamic imbalance between the repair and destruction of joint tissues [3,4]. In the knee, this is characterized by pathology involving the whole joint, including cartilage degradation, bone remodeling, osteophyte formation, menisci tears, and synovial inflammation [3,5], with a complex biological response involving biomechanics, inflammation, and the immune system [3,6].

KOA manifests in usage-related pain and/or functional limitation [7]. The pain experience typically transitions over time from intermittent weight-bearing or inflammatory pain to a more persistent, chronic pain [8,9]. Risk factors for the development of knee OA include age, joint injury, malalignment and other mechanical factors, sex, obesity, metabolic syndrome (in particular, diabetes mellitus), and genetic predisposition [4,10].

Pain is the major impairment for people with OA, but its etiology is complex. It is characterized by nociceptive and neuropathic components [11], and involves both peripheral and central pain sensitization mechanisms [12]. These components of pain vary between and within individuals and are challenging to assess in routine practice [9]. Understanding the mechanisms of pain is further hindered because structural joint damage seen on X-rays correlates poorly with symptomatic pain in OA [9]. Findings from magnetic resonance imaging (MRI) are conflicting [13], though innervated tissues demonstrate pain associations [14]. Furthermore, after removing damaged tissue by total knee arthroplasty (TKA), around 20% of patients with KOA continue to experience chronic pain [15], supporting the involvement of a multifactorial etiology [16].

2. Current treatment of OA pain

Proposed clinical phenotypes of KOA are associated with pain sensitization, psychological distress, radiographic severity, increased body mass index, decreased muscle strength, inflammation, and comorbidities [17], though to date these have not led to stratified interventions. The heterogeneity in clinical phenotypes has likely hampered the development of a one-size-fits-all therapy for an unselected patient population [17] and there are currently

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Article highlights

- There is an urgent need to develop new therapies and new management approaches for pain associated with KOA.
- The TRPV1 receptor is expressed in a subset of nociceptive sensory neurons and plays an important role in pain transmission and regulation.
- In the structures of the knee joint, nociceptors are present in abundance and in KOA, increased expression of TRPV1 is seen in the synovium, bone, and cartilage.
- This provides a rationale for targeting TRPV1-expressing nociceptors in the knee to modulate activity locally at the origin of the pain pathway in KOA.
- This approach may avoid side effects and limited efficacy seen with currently available analgesics.
- This narrative review summarizes the potential for targeting the TRPV1 pathway to treat pain in KOA, and summarizes progress made in developing TRPV1 modulators for KOA.

no disease-modifying therapies to prevent KOA or to slow the progression of joint damage [4]. Current pharmacological treatments for OA focus on relieving pain symptoms. Patients typically receive topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) initially, with the addition of intra-articular (IA) corticosteroid (CS) or IA hyaluronic acid (HA) (variably recommended in guidelines) [5,18]. Inadequate pain relief is common (>50%) in patients with KOA requiring analgesics [19].

Treating the inflammation in KOA with oral NSAIDs improves pain, physical function, and stiffness [20], but has been associated with substantial gastrointestinal, renal, and cardiac adverse events (AEs), making them unsuitable for many patients [21] (in particular, the elderly), though topical formulations can reduce risk for systemic adverse events. Several therapies used successfully to treat other inflammatory diseases have not shown overall benefit for KOA; for example, the tumor necrosis factor-alpha (TNF-α) inhibitor adalimumab administered subcutaneously [22], the interleukin-1 (IL-1) receptor antagonist anakinra administered IA [23], and the orally administered anti-inflammatory agent colchicine [24] have not been beneficial for OA pain. Methotrexate, which exerts anti-inflammatory effects via multiple signaling pathways [25], is not currently recommended for use in KOA [5], though has recently shown a moderate but potentially clinically meaningful effect on reducing pain in patients with hand OA and MRI-detected synovitis, providing proof-of-concept that methotrexate might have a role in the management of hand OA with an inflammatory phenotype [26].

Opioids, which act centrally, decrease pain intensity and improve function in patients with OA, but the benefits observed are small, while AEs and the risk of addiction limit their usefulness in the long-term treatment of OA of the hip or knee [27]. Therefore, they are not uniformly recommended in treatment guidelines for KOA [4].

Most available guidelines for KOA do not advocate for IA injections until the second or third line due to their invasive nature, and potential for complications [28]. IA CS injections are typically reserved for KOA patients not responding to oral or topical analgesics [4]. Although, IA CS therapy provides short-term symptomatic benefits in KOA, long-term benefits seem to be less likely, even when administered in combination with other IA therapeutics [28]. Although the use of viscosupplementation with IA HA in KOA has been extensively researched [28], views on its efficacy still vary [29]. Variations in HA formulations, different periods of follow-up, and differences in injection schedules and IA techniques may contribute to the heterogeneity in effect sizes observed in published trials for IA HA [28].

Given the limitations of existing treatments, there is an urgent need to develop new therapies and management approaches for pain associated with KOA. The progression to chronic pain in patients with OA appears to involve changes in joint innervation, and sensitization involving the joint, dorsal root ganglion (DRG) and central nervous system (CNS) [30]. Therefore, a rational approach is to target the pain pathway itself: focusing on the nociceptor where pain is generated [31,32].

3. Changing direction in OA pain therapy: targeting nociception

Within the joint, nociceptive inputs are amplified by pronociceptive and inflammatory molecules which sensitize and/or activate sensory nerves [16]. For example, in the hip joints of patients with painful OA, an increased density of nerve fibers immunoreactive for substance P and calcitonin-gene related peptide (CGRP) in both soft tissue and the hip joint capsule synovial layer relative to levels in non-OA controls (patients with femoral neck fractures) was observed [33]. In patients with painful KOA, substance P- and CGRP-immunoreactive-free nerve fibers were more abundant in medial sites in the knee affected by OA than in OA non-affected lateral and suprapatellar sites in the same joint [34]. In further studies of synovial tissue from patients with knee OA, expression of growth associated protein-43 (a marker of regenerating nerve fibers), substance P, CGRP, and tyrosine hydroxylase (a marker of dopaminergic neurons) were all significantly increased in biopsies from the medial joint compartment where patients' pain was predominant relative to biopsies from lateral compartments of their knees [35]. Lastly, although articular cartilage is considered to be avascular and aneural in healthy adults, neovascularization with accompanying neoinnervation is observed in knee cartilage of patients with advanced KOA [36], adding to the evidence suggesting that in OA neuronal remodeling occurs in different joint tissues and is associated with disease progression.

Nerve growth factor (NGF) inhibitors were the first molecules to target pain signaling pathways in KOA. These antibodies were administered subcutaneously. NGF is a key mediator of acute and chronic pain, with pro-algesic effects which include sensitization of peripheral nociceptive terminals and sprouting of sensory nerves [37]. Although several monoclonal antibodies (mAbs) designed to inhibit the binding of NGF to its high-affinity cognate receptor tropomyosin receptor kinase A (TrkA) reached advanced clinical trials for OA pain, their development was discontinued due to safety concerns [38–41].

The 2021 Nobel Prize in Physiology or Medicine recognized the discoveries of receptors for temperature and touch, including

the transient receptor potential vanilloid 1 (TRPV1) receptor, which can be activated by exogenous stimuli to generate pain signaling [42]. TRPV1 is a calcium ion (Ca^{2+}) permeable, nonselective cation channel vital for detecting noxious chemical and physical stimuli known to cause irritation and pain (e.g. heat, acid, and capsaicin) [43]. A growing understanding of the roles played by TRPV1 in pain transmission has led to the evaluation of TRPV1 modulators for treating conditions involving chronic pain, including KOA [44,45].

4. Role of TRPV1 in pain pathways

Since the 1960s there has been awareness of the excitatory effects of capsaicin, the main pungent component in 'hot' chili peppers, on neurotransmission, nociception, and pain. It was not until 1997 that the *TRPV1* gene was cloned and TRPV1 functionally identified as the receptor activated by capsaicin in nociceptive neurons [46,47].

TRPV1 has a tetrameric structure with six transmembrane domains and a pore-forming hydrophobic stretch linking segments 5 and 6 (Figure 1). The channel contains multiple phosphorylation sites, allowing for its activity to be regulated by various kinases, including protein kinase A, protein kinase C, Ca^{2+}/calmodulin-dependent protein kinase II, sarcoma kinase, and the Ca^{2+}-dependent phosphatase, calcineurin [48]. TRPV1 is activated by noxious stimuli (heat above ~42°C, mechanical stress, low pH [<6.5]), or by algogenic endogenous and exogenous ligands including capsaicin, resiniferatoxin (RTX), and growth factors [47,49]. Detailed mechanisms and descriptions of binding sites have been characterized for only a few endogenous agonists of TRPV1 [50].

TRPV1 is predominantly expressed in the neurons of the peripheral nervous system (PNS) and CNS [47]. In the PNS, TRPV1 is primarily expressed in small- and medium-diameter nociceptive neurons in the DRG, nodose ganglia, sympathetic ganglia, and trigeminal ganglia [47]. These neurons form unmyelinated C and myelinated Aδ sensory nerve fibers that project to most organs and tissues [49]. Once activated, these nerve fibers transmit noxious signals to secondary neurons in the spinal cord dorsal horn and from there to the brain, which registers the signal as acute discomfort or pain [51] (Figure 2). In the CNS, TRPV1 is expressed in the laminae I and II of the spinal cord and dorsal horn, where it is involved in synaptic transmission/modulation of peripheral nociceptive input [47].

In the absence of peripheral inflammation, TRPV1 is synthesized in the cell bodies of primary sensory neurons in the DRG and transported both to peripheral and central terminals, contributing to heat sensitivity in the periphery [52]. Following tissue injury or inflammation, NGF and TrkA interact with TRPV1 in peripheral sensitization of nociceptors [41]. NGF produced in inflamed tissue binds to TrkA localized to peptidergic sensory nerves. This NGF-TrkA complex is internalized and retrogradely transported along the axon to the cell body in the DRG, where it increases TRPV1 phosphorylation [41]. This, in turn, increases TRPV1 translation, with TRPV1 anterogradely transported along the axon to the peripheral nociceptor terminal, where it contributes to the maintenance of inflammatory heat pain hypersensitivity [52]. This may explain the increase in TRPV1 immunoreactivity seen in synovial tissue from people undergoing TKA for OA relative to levels in postmortem samples from individuals without a history of knee pain [53]. In patients undergoing TKA, TRPV1 overexpression has also been observed in the bone and the cartilage of OA joints [54].

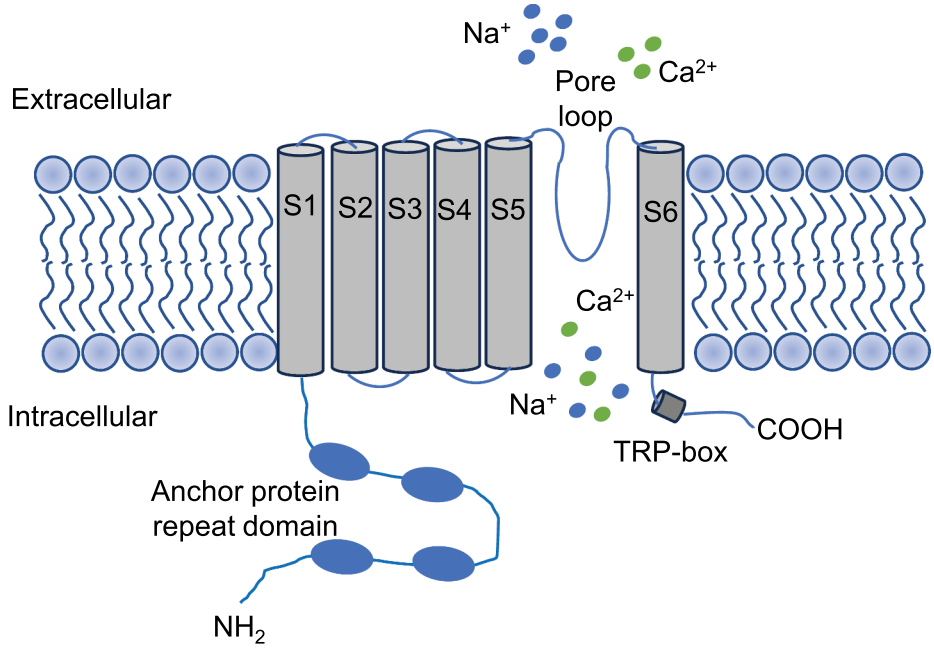

Figure 1. Structure of TRPV1.

The *N*- and C-termini of TRPV1 are separated by six transmembrane structural domains (S1–S6). The N-terminal plays a role in the sensitivity of the channel to activators and has an anchor protein repeat structural domain. The C-terminus has a conserved TRP-box near the sixth transmembrane structural domain which affects channel stability and function. The pore loop is sited between S5 and S6. When TRPV1 is activated, the structure of S5–6 is altered, allowing Ca^{2+} influx.

S, structural domain; TRP, transient receptor potential; TRPV1, transient receptor potential vanilloid 1.

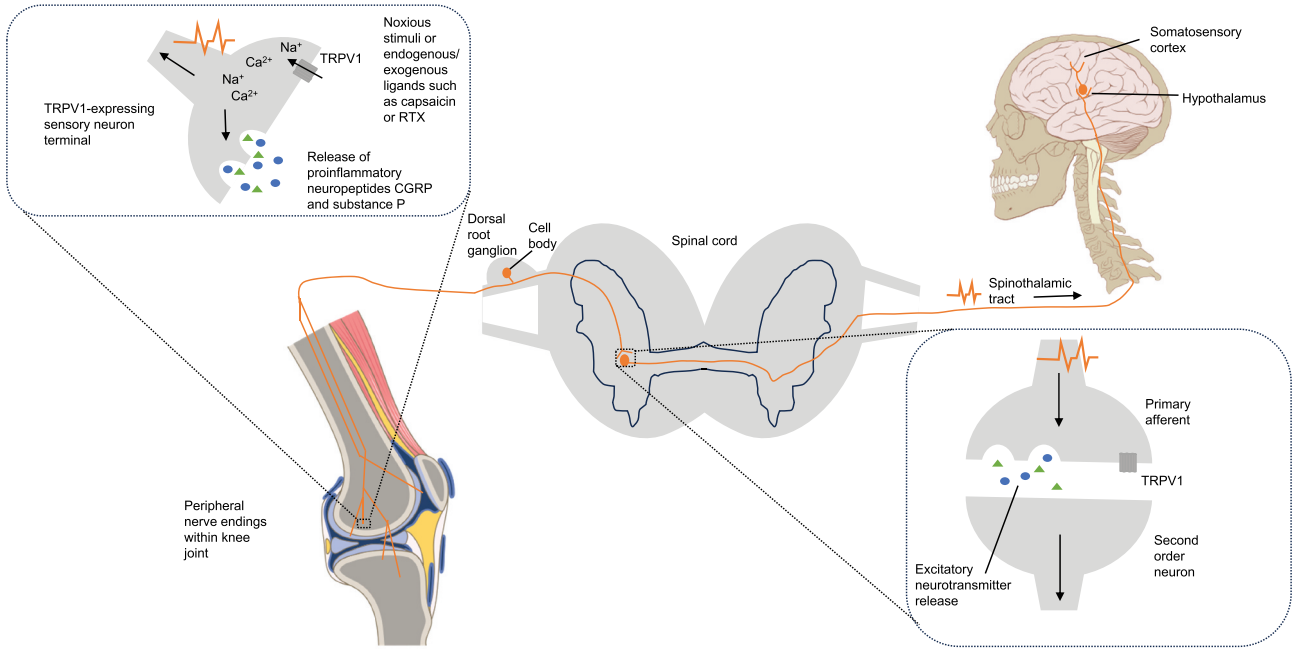

Figure 2. Pain transmission via TRPV1 in the PNS and CNS.

Activation of TRPV1 by noxious stimuli or ligands enables sodium (Na^+) and calcium (Ca^{2+}) influx through voltage-gated Ca^{2+} channels, leading to depolarization and propagation of action potentials for transmission into the CNS, while also triggering local release of proinflammatory neuropeptides. In the central terminals of the TRPV1-expressing nociceptors, the TRPV1 channel amplifies and modulates neurotransmitter release in the spinal cord. The spinothalamic tract relays the signal to the brain, where the thalamus passes the nociceptive signal to the cortical area which registers this message as acute discomfort or pain.

CGRP, calcitonin gene-related peptide; CNS, central nervous system; PNS, peripheral nervous system; RTX, resiniferatoxin; TRPV1, transient receptor potential vanilloid 1.

In TRPV1-expressing neurons, TRPV1 activation by agonists like capsaicin, heat, and protons triggers the release of proinflammatory neuropeptides like substance P and CGRP, resulting in neurogenic inflammation via a biochemical cascade [45]. Recently, human subjects carrying a homozygous mutation rendering the TRPV1 channel nonfunctional were found to have no sensitivity to capsaicin applied to the mouth or skin. They exhibited an elevated cold-pain threshold and extensive neurogenic inflammatory, flare, and pain responses following the application of mustard oil, providing direct evidence that pain-related functional changes are linked to TRPV1 [55].

Outside the PNS and CNS, accumulating data suggest that TRPV1 is also expressed in almost all types of mammalian immune cells, including dendritic cells, macrophages, lymphocytes, and neutrophils [56], and is implicated in regulating immune responses [44,56,57]. Therefore, modulating TRPV1 for pain relief may also influence immune pathways involved in pathogenesis [58].

4.1. TRPV1 modulation in pre-clinical models of non-OA pain

Cloning of the *TRPV1* gene led to investigations using *in vivo* pharmacological approaches and *TRPV1* gene knockdown in mice, which supported a critical role of this channel in nociceptive, inflammatory, and neuropathic pain [48,51]. Modulation of TRPV1 in such studies has validated TRPV1 as a therapeutic target in preclinical models of chronic pain, including cancer, neuropathic, postoperative, and musculoskeletal pain [59].

TRPV1 is involved in both afferent (sensation of pain) and efferent (neurotransmitter and neuropeptide release) functions and can mediate both inflammation and pain [45]. Gene knockout mice lacking the TRPV1 channel have impaired nociception and pain sensation [60]. Mustard oil (used as an irritant to induce pain and inflammation) activates mouse and human recombinant TRPV1, as well as TRPV1 channels in mouse sensory neurons [61]. In rats with chronic constriction injury (CCI) of the sciatic nerve, intrathecal injection of TRPV1 small interfering RNA (siRNA) led to a marked downregulation of spinal TRPV1 expression and attenuation of the pre-treatment level of neuropathic pain [62]. In a rat model of bone cancer pain, intrathecal administration of siRNA against TRPV1 ameliorated mechanical allodynia and thermal hyperalgesia induced by tumor cell implantation [63]. The reductions in nociception observed in this model were accompanied by significant suppression of neuro-inflammatory markers in the spinal cord (class I histone deacetylates and TNF-α) [63].

Two main pharmacological approaches have been pursued to modulate TRPV1 for treating pain: antagonists and agonists [64], although the results observed using these two approaches have differed.

4.1.1. TRPV1 antagonists

Early studies establishing TRPV1 as a key channel in peripheral sensitization associated with inflammation and injury rationalized the development of specific antagonists of TRPV1 as potential analgesics [65]. TRPV1 antagonists were found to be analgesic in animal pain models [66,67]. For example, a single intrathecal injection of SB366971 significantly reduced postoperative hypersensitivity in a rat plantar incision model

[68]. Although TRPV1 antagonists provide useful insights into mechanisms controlling pain, their clinical use has been limited by detrimental side effects, such as elevating body temperature (hyperthermia) and reducing the ability to sense noxious heat (thermal hypesthesia) leading to burn injuries [48,59]. So called 'thermoneutral' TRPV1 inhibitors have shown analgesic potential *in vitro* [69], but their potential as analgesics has yet to be validated in clinical studies [45].

4.1.2. TRPV1 agonists

Capsaicin is a highly selective and potent (low nanomolar affinity) exogenous agonist for the TRPV1 receptor [70]. Initially, capsaicin binding to TRPV1 leads to channel opening, allowing Ca^{2+} and Na^{+} entry and nerve depolarization, stimulating substance P release and swiftly producing hypersensitization with an intense burning and stinging sensation, followed by a long-lasting nerve desensitization at the site of administration [71]. The dose level of capsaicin is critical in determining the duration of its analgesic effect. Following exposure to a low dose of capsaicin, specific desensitization is observed, whereby the TRPV1 receptor shows a reduced response specific for capsaicin, but not for other irritants. This functional impairment of the receptor (with blockade of mechanotransduction, nerve firing, and conduction) results in weak transient analgesia [65]. Stimulation of TRPV1 with a high therapeutic dose of capsaicin, or repeated stimulation with a low dose of capsaicin, results in a reversible desensitization in which the previously excited neurons remain unresponsive to further challenge. Reversible deactivation of the axonal terminals of TRPV1-expressing afferents contributes to a long-lasting analgesic effect [65].

Among the known endogenous and synthetic agonists for TRPV1, RTX, which is derived from the plant *Euphorbia resinifera*, has the highest potency [49]. Similar to the mechanism of action of capsaicin, binding of RTX to TRPV1 results in a reversible deactivation of the peripheral terminals of TRPV1-expressing nociceptors, that can lead to prolonged analgesia [49,72]. In cell-based studies, RTX was 500–1000 times more potent than capsaicin in desensitizing rat urinary bladder primary afferents to a subsequent challenge with capsaicin than capsaicin itself [73]. Confocal imaging of nociceptive neurons expressing TRPV1 shows that RTX treatment induces vesiculation of the mitochondria and the endoplasmic reticulum within around 1 min and nuclear membrane disruption within 5–10 min [74]. The action of RTX is thought to be due to a combination of Ca^{2+} overload and osmotic injury [75]. At the cellular level, the presence of TRPV1 is critical for this RTX action: exposure of non-TRPV1-expressing cells to RTX at concentrations 1,000 times above those that can cause lesions within TRPV1-expressing cells does not appear to produce any negative effects [49]. In animal models, the analgesic effects of RTX on TRPV1-expressing axonal terminals are reversible over time [72,76]. After hind paw injections in rats, RTX-induced attenuation of TRPV1-expressing Aδ- and C-fibers led to thermal hypoalgesia lasting for up to 10 weeks. The return of behavioral pain responses corresponded with the expression of nerve regeneration markers in the TRPV1-expressing Aδ- and C-fibers [72]. Similarly, in a mouse model of sensory neuropathy, intraperitoneal injection of RTX induced a transient hypoalgesia by day 7, with mechanical and thermal nociception restored by day 28 post-treatment [76].

4.2. TRPV1 modulation in pre-clinical models of OA-related pain

When considering TRPV1 modulation in the context of a potential role in OA pain, it is worth noting the following: KOA pain involves both the nerves that innervate the soft tissues of the joint and those that innervate the underlying subchondral bone and surrounding soft tissues [31]; in the structures of the knee joint, nociceptors are present in abundance [10,77] (innervation is absent in healthy cartilage, but neoinnervation of cartilage is observed in advanced KOA [36]); although only a subset of the sensory neurons in the knee express TRPV1 [78], increased expression of TRPV1 is seen in synovial tissue [53], bone, and cartilage [54] of patients with advanced KOA (Figure 3).

In mice, at the level of the DRG, ~40% of articular afferents from the knee and ankle joints express TRPV1 and the majority of these are peptidergic (as shown by simultaneous immunostaining for CGRP) [78]. This subset-specific expression means that IA administration of a TRPV1 modulator, such as RTX, would not be expected to target every afferent nerve in the knee joint. This contrasts with the anti-NGF mAbs discussed earlier, which theoretically target a broader population of sensory afferents (in rat DRG neurons, strong immunoreactivity for the NGF receptor TrkA is seen for all nociceptive neurons, i.e. Aα-, Aβ-, Aδ-, and C-fibers, likely reflecting the profound influence of NGF on these neurons [79]).

In a rat model of OA pain, TRPV1 protein expression was shown to be upregulated in the cell bodies of afferent fibers innervating the knee joint [80]. In the mouse monoiodoacetate (MIA) model, which induces some features also seen in human OA joint pathology and is associated with robust pain behavior responses, levels of the endogenous TRPV1 ligand 12-hydroxyeicosatetraenoic acid were elevated in the knee joint but not in the DRG or spinal cord, and there was increased TRPV1 expression in the knee joint synovium following injection of MIA [53]. In a rat model, pre-treatment with IA capsaicin (0.5%) 2 weeks before MIA injection prevented mechanical pain over the 4 weeks following MIA treatment and significantly reduced chronic joint pathological changes, such as bone erosion and trabecular damage, relative to pain and joint alterations seen in control animals which had not been pre-treated with capsaicin [81]. Analgesic effects were also observed in rats with MIA-induced OA following a single IA administration of RTX (0.0003% to 0.03%). RTX increased paw withdrawal latency to radiant noxious heat and mechanical stimuli for 3–10 days and reduced the time that animals used for weight bearing on the contralateral limb [82]. In dogs with naturally occurring OA, a single 10 µg IA injection of RTX produced suppression of pain and improved gait and weight bearing for 4 months or longer [83].

Synovial macrophages involved in OA symptoms and progression become polarized into either M1 or M2 subtypes in OA synovial tissues, synovial fluid, and peripheral blood, and the activation state and the M1/M2 ratio of these

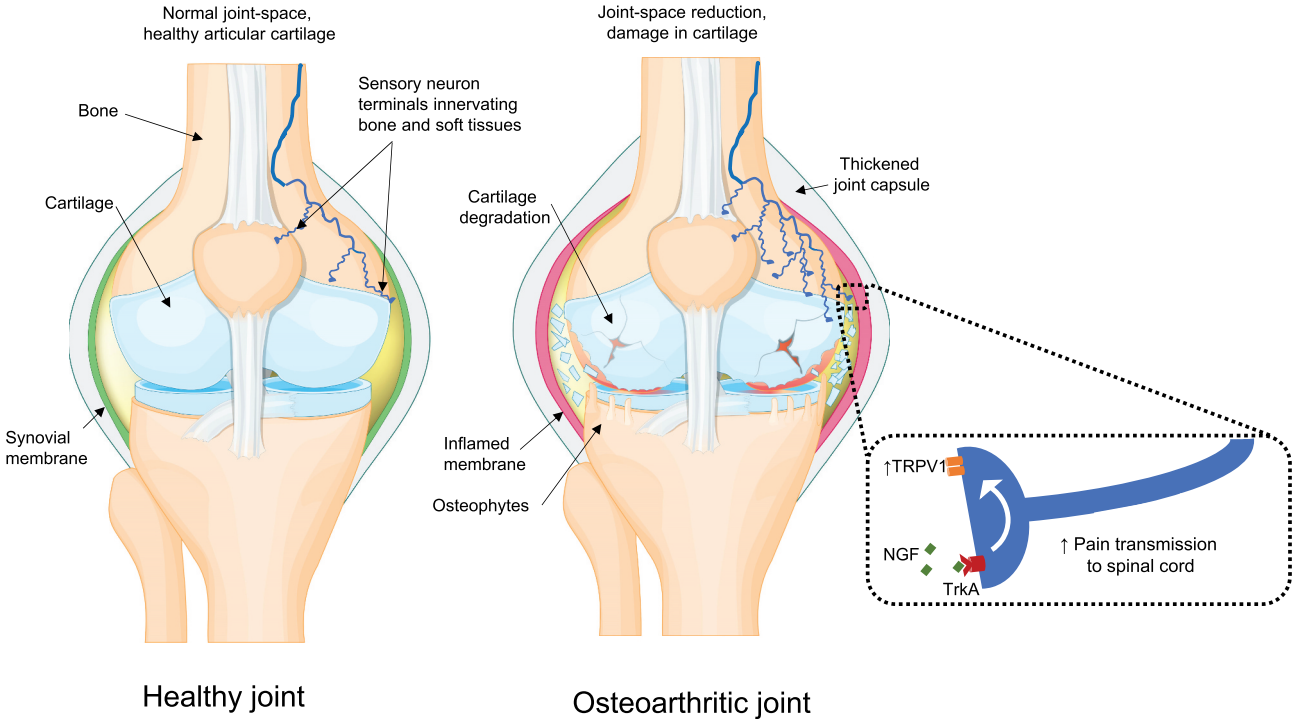

Figure 3. Changes in joint innervation accompany the development and progression of KOA.

As KOA develops there is an increase of sensory nerve fiber innervation in the bone and surrounding soft tissues of the joint, with neoinnervation of cartilage in advanced KOA. In addition, concentration of sensory neuropeptides in synovial fluid increases with increasing OA severity. Increased NGF expression in subchondral bone and synovium is associated with OA knee pain, and NGF binding to TrkA on sensory nerve terminals leads to increased expression of TRPV1 and peripheral sensitization of TRPV1-expressing nociceptors.

KOA, knee osteoarthritis; NGF, nerve growth factor; OA, osteoarthritis; TrkA, tropomyosin receptor A; TRPV1, transient receptor potential vanilloid 1.

macrophages is strongly associated with OA severity [84]. In both human and rat OA synovium, TRPV1 expression and M1 macrophage infiltration were simultaneously increased, with >90% of infiltrating macrophages expressing TRPV1. In a rat OA model, treatment with IA capsaicin improved knee swelling, synovitis score, and reduced M1 macrophage level [85]. In the destabilization of medial meniscus-induced model of OA in mice, IA capsaicin activated TRPV1 in the articular cartilage resulting in significant cartilage-protective effects, including reduced cartilage erosion and Osteoarthritis Research Society International (OARSI) score, increased chondrocyte count, improved total cartilage thickness, and reduced ferroptosis [86]. Chondroprotective and anti-ferroptic effects were also observed for capsaicin in *ex vivo* cartilage explants from OA patients [86].

4.3. Clinical trials of TRPV1 modulators in non-OA pain conditions

4.3.1. TRPV1 antagonists

Within a decade of cloning the *TRPV1* gene, the first potent, small-molecule antagonists of TRPV1 entered phase I/II clinical trials in chronic inflammatory pain and migraine [87]. Among the first generation of TRPV1 antagonists tested, the duration and magnitude of the febrile reaction varied significantly. For example, 30 mg and 95 mg oral doses of the piperazine AZD1386 increased body temperature by around 0.4°C and 0.7°C on average, respectively [88], whereas 2, 8, and 15 mg oral doses of the pyrimidine AMG517 caused temperature elevations up to 40.2°C lasting 1–4 days [89].

To avoid the undesirable effects on body temperature seen with early TRPV1 channel antagonists, several modality-specific inhibitors were developed with the intention of selectively activating the receptor via binding without interrupting its nociceptor function or altering body temperature. For some of these compounds, such as AMG-8562, although testing in animal models showed promise [90], their pharmacological profile in humans was found to differ [89], so clinical development was not pursued.

4.3.2. TRPV1 agonists

Clinical development of TRPV1 agonists for pain relief has advanced further than that of TRPV1 antagonists. Creams, lotions, and patches containing low (<1%) concentrations of capsaicin for daily skin application for the relief of neuropathic and musculoskeletal pain have been available in many countries since the early 1980s. These are often sold as over-the-counter, self-administered medications [91]. The safety and modest efficacy of low-concentration capsaicin formulations are supported by meta-analyses [92,93]. Nevertheless, factors such as the need for frequent (3–5 times daily) and prolonged (at least 2 weeks) application, inconvenience of the product rubbing on to clothes/bedding, and a burning sensation upon application are believed to negatively affect compliance among patients and hence the efficacy of these preparations [91].

The development of a topical patch containing a high concentration of capsaicin (8%) addressed several of these drawbacks. The capsaicin 8% topical system was first approved by the U.S. Food and Drug Administration (US FDA) in 2009 and in

the U.S.A. this product is now indicated in adults for the treatment of neuropathic pain associated with postherpetic neuralgia (PHN) and for neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet [94]. In the EU, this product is indicated in adults for treating peripheral neuropathic pain [95].

The high-concentration capsaicin patch has a longer duration of effect vs low-concentration topical formulations [91]. Because the active agent is administered during a single application under the supervision of a physician or HCP, this removes the potential for variability in administration and a lack of patient compliance [91]. A single 30- or 60-min application to the skin in patients with peripheral neuropathic pain produces effective pain relief for up to 12 weeks, and if the pain persists or returns, treatment can be repeated every 90 days [94,96]. Furthermore, capsaicin is primarily metabolized by cytochrome P450 (CYP450) enzymes in liver microsomes [97] and data collected from CYP450 inhibition and induction studies indicate that topically administered capsaicin is unlikely to alter the systemic metabolism of concomitant medicines [98].

The effect of capsaicin on nerve terminals can be observed in skin biopsies of treated individuals: in one study, 3 weeks of topical low-dose capsaicin (0.075%) treatment resulted in ~80% epidermal denervation [98]. In another study, a single 60-min application of high-dose capsaicin (8%) produced ~60% epidermal denervation [99]. The precise mechanism by which capsaicin disrupts TRPV1-expressing nociceptive terminals has not been fully elucidated [100], although recent studies in mice suggest capsaicin-induced depolymerization of axonal microtubules is involved [101].

In PHN, the capsaicin 8% topical patch was evaluated in two 12-week, double-blind, randomized, dose-controlled, multicenter, phase III studies (ClinicalTrials.gov identifiers NCT00115310 and NCT00300222) [102,103]. The primary endpoint in both studies was the change in mean numeric pain rating scale (NPRS) scores from baseline to weeks 2–8 in patients with PHN randomized to receive a single 60-min application of the 8% capsaicin 8% patch or a capsaicin 0.04% control patch. The studies found that a single 60-min application of the capsaicin 8% patch provided a rapid and significant reduction in pain that was maintained over the 12-week period. Most treatment-emergent AEs were application-site specific (notably, erythema, and pain), transient, and generally mild to moderate in severity [102].

The efficacy and safety of the capsaicin 8% patch was also evaluated in a 12-week study versus placebo patch (NCT01533428) in 369 patients with painful DPN (PDPN). The percentage reduction in average daily pain score from baseline to between weeks 2 through 8 (the primary end point) was statistically significant for capsaicin 8% patch versus placebo (−27.4% versus −20.9%; $p = 0.025$); improvements in pain were observed from week 2 onward. Apart from application site reactions, treatment-emergent AEs were similar between groups [104].

Two phase 3/4 long-term safety trials evaluated the safety and efficacy of repeated application of the capsaicin 8% patch in patients with PDPN (PACE [NCT01478607]) and in non-PDPN populations, i.e. patients with painful Human Immunodeficiency Virus – associated neuropathy (HIV-AN), post-traumatic or post-surgical nerve injury, or PHN (STRIDE; [NCT01252160]) [105]. In these trials, the capsaicin 8% patch demonstrated consistent and reproducible efficacy and tolerability over a 52-week period in these patient populations [94].

Several trials in patients with lower urinary tract symptoms due to interstitial cystitis or detrusor overactivity have shown that intravesical RTX significantly reduced bladder pain (average visual analog scale [VAS] pain scale reduction 0.42 on RTX treatment, $p = 0.02$), with no significant improvement observed in frequency, nocturia, incontinence, or first involuntary detrusor contraction [106]. The mechanism of pain relief in the bladder is unclear, although desensitization of bladder afferent C fibers after binding to RTX, inhibition of release of neuropeptides such as CGRP and substance P, and downregulation of TRPV1 expression in bladder C fibers may be involved [106].

4.4. Clinical trials of TRPV1 modulators in OA-related pain

4.4.1. Trials of TRPV1 antagonists

A phase IIb dose-finding trial evaluated the TRPV1 antagonist AZD1386 in patients with KOA pain that was insensitive to NSAIDs. The trial used an adaptive design and at interim analysis, the study was halted for futility as AZD1386 showed no significant pain decrease based on the primary endpoint variable (changes in the Western Ontario and McMaster Universities arthritis index [WOMAC] pain scale from baseline to mean of weeks 2 and 4) [107]. Among other TRPV1 antagonists that progressed into clinical trials, NEO6860 was evaluated in a randomized, double-blind, three-period crossover, phase II study that compared 1 day (two doses) of NEO6860 (500 mg twice daily as an oral solution), placebo, and oral naproxen in 54 patients with pain due to KOA. Although NEO6860 was found not to be hyperthermic in this exploratory study, it did not statistically outperform placebo and had a less favorable safety profile compared with naproxen or placebo [108].

In a multiple-dose, double-blind, randomized, phase I study of another TRPV1 antagonist, 18 patients with KOA received JNJ-39439335 (mavatrep) treatment administered once-daily orally at 10, 25, or 50 mg for 21 days [109]. Responder analysis revealed that 67% of the participants in the 10 mg dose group, and all participants (100%) in the 25 mg and 50 mg dose groups showed at least a 30% reduction in stair climbing – induced pain intensity scores at the end of the dosing period compared with 50% of participants in the placebo group. However, no statistically significant differences from baseline were detected for the assessment of pain using a modified WOMAC questionnaire, and there was a marked dose-related increase in the heat pain perception threshold and heat pain latency in all participants treated with JNJ-39439335 (44% of participants reported feeling hot, 44% reported thermohypoesthesia, 44% reported paresthesia, and 33% reported feeling cold) [109].

4.4.2. Trials of TRPV1 agonists

In 2010, Health Canada approved a topical 0.075% zucapsaicin cream (zucapsaicin is a synthetic cis-isomer of capsaicin and is

also referred to in the literature as civamide [cis-8-methyl-N-vanillyl-6-nonenamide]) as an adjunct to oral anti-inflammatory agents (cyclooxygenase-2 [COX-2] inhibitors or NSAIDs) for the relief of severe pain in adults with KOA [110]. Two IA-administered TRPV1 agonists, CNTX-4975 and RTX, have advanced into phase III studies for the treatment of pain associated with KOA and have received fast track designation [111] and breakthrough therapy designation [112], respectively, from the US FDA in this indication. Lastly, a separate IA RTX development program also reported positive phase IIa results in moderate-to-severe OA of the knee [113].

Double-blind randomized controlled trials have evaluated capsaicin and zucapsaicin in topical formulations ranging from 0.025% to 0.075% for the treatment of painful OA of the knee [114–116], hand [117], and a mix of joints [118]. These studies found that topical capsaicin treatment four times daily is moderately effective in reducing pain intensity up to 20 weeks regardless of the site of application and dose in patients with at least moderate pain and clinical or radiologically defined OA. In these trials, topical capsaicin was reported as being well tolerated, with no systemic toxicity. Transient application site burning affected 35–100% of the treated patients, with incidence rates declining over time [119].

The mechanism of action of zucapsaicin is similar to that of capsaicin [120] and topical zucapsaicin also localizes at the area of application and displays low systemic absorption [121]. In a randomized phase III clinical trial, patients aged between 40 and 76 years with OA of the knee received zucapsaicin 0.075% cream, or a lower dose zucapsaicin 0.01% cream as a control, applied three times daily to their target knee for 12 weeks, with a 52-week open-label extension (OLE) (NCT00077935) [115]. Zucapsaicin 0.075% cream showed statistically significant and clinically relevant benefits over zucapsaicin 0.01% cream in each of the three co-primary endpoints (WOMAC pain subscale, WOMAC physical function subscale, and the Subject Global Evaluation) between baseline and Day 84. Efficacy was maintained in the 52-week OLE. The most common AE was a self-limited burning sensation at the application site (reported by 18% of patients on the first day of treatment in the double-blind trial) that was most often mild to moderate in severity and transient [115].

Despite topical zucapsaicin 0.075% cream gaining the previously mentioned approval from Health Canada in 2010 for use in adults with KOA, a new drug application to the US FDA for this indication [122] was not successful. Although topical capsaicin is conditionally recommended by the American College of Rheumatology/Arthritis Foundation for treating knee OA [5], OARSI recommends against its use due to the poor quality of evidence available [18]. Other factors limiting its use may include uncertainty over whether a lipophilic/hydrophobic agent such as capsaicin or zucapsaicin applied topically at low concentrations penetrates the synovial fluid of the knee joint at sufficient concentration to provide a meaningful benefit against pain associated with KOA [100], the higher cost relative to topical NSAIDs [123], and the need for frequent reapplication to maintain efficacy [119]. Use of a higher potency topical formulation may address some of these challenges, for example in a phase II study (NCT03528369), CGS-200-5 (a topical liquid formulation containing 5% capsaicin) applied for 1 hour on four consecutive days significantly improved WOMAC pain scores relative to placebo ($p = 0.02$), and post-hoc analyses showed this improvement was maintained over 3 months. The treatment was well-tolerated and application site pain decreased with each consecutive dosing day [124].

IA formulations provide an alternative approach to overcome the challenges associated with topical application of TRPV1 agonists. These formulations have progressed into advanced clinical development, with developments focused on two IA TRPV1 agonists: CNTX-4975 and RTX.

CNTX-4975 is a highly potent, purified synthetic trans-capsaicin [21]. A dose-ranging, placebo-controlled, randomized, double-blind, phase IIb study (TRIUMPH; NCT02558439) was conducted to examine the effects of this TRPV1 agonist administered into the knee joint [125]. Adults with stable KOA were randomized in a 2:1:2 ratio to receive a single IA injection of placebo, CNTX-4975 0.5 mg, or CNTX-4975 1.0 mg. The primary endpoint was the area under the curve (AUC) for change from baseline in daily WOMAC pain score with walking score through week 12. At the week 12 follow-up, decreases in the AUC for the pain score with CNTX-4975 in the 0.5 mg and 1.0 mg groups were higher than for placebo (least-squares mean difference [LSMD] for the 0.5 mg group was −0.79, $p = 0.0740$; and for the 1.0 mg group was −1.6, $p < 0.0001$). These significant improvements were maintained in the 1.0 mg group at week 24 (LSMD −1.4, $p = 0.0002$). The incidence and severity of treatment-emergent AEs were comparable in the placebo and CNTX-4975 1.0 mg groups [125].

Based on the findings from the TRIUMPH study, CNTX-4975 was further evaluated in a program of phase III studies conducted in the U.S.A.: VICTORY-1, −2, and −3 (NCT03429049, NCT03660943, and NCT03661996, respectively). Summary results posted to the ClinicalTrials.gov registry for these studies (full results had not yet been published at the time of writing) indicate that the primary endpoint was not met in the VICTORY-1 and VICTORY-2 randomized, double-blind, placebo-controlled, 52-week studies [126,127]. These studies had KOA pain-related primary endpoints, i.e. change from baseline in average weekly pain with walking (NPRS 0–10) in the index knee at week 12 in VICTORY-1; and change from baseline in WOMAC A at week 12 in VICTORY-2. In both studies, the CNTX-4975 and placebo arms showed reductions from baseline in pain scores evaluated for the primary endpoint [126,127], which is consistent with observations of an IA placebo effect in published findings from other trials of KOA treatment [128]. The third phase III study, VICTORY-3, was an open-label, 8-week study comparing the comfort and ease of use of five different treatment regimens for IA CNTX-4975 in subjects with chronic, moderate-to-severe OA knee pain [129]. In this study, the most effective regimen in controlling pain associated with IA injection involved cooling the subject with an Elasto-Gel circumferential knee wrap for 40 min before IA lidocaine injection, followed by 10 min before the CNTX-4975 injection, and for at least 10 min and up to 90 min after the CNTX-4975 injection as needed [129].

Two companies have reported data from separate trial programs for IA RTX in KOA [112,113]. In the first of these programs, a phase Ib double-blind study assessed the safety, tolerability, and efficacy of IA RTX or IA placebo for the treatment of

moderate-to-severe pain due to OA of the knee [130]. Efficacy for RTX at 5, 12.5, 20, and 30 µg dose levels was assessed using the subject-reported WOMAC and NPRS pain scores. The difference in the mean score for WOMAC A1 (pain on walking on flat surface) at week 12 between the placebo subjects and RTX-treated subjects, expressed as the LSMD in change from baseline relative to placebo, ranged from −0.04 to −2.63 points depending on the dose level cohort. By mixed model repeated measures analysis, pain reduction at 12 weeks was highest for the 12.5 µg dose versus placebo: LSMD of −2.63 by WOMAC A1 score ($p = 0.0311$, $n = 6$) and −14.58 by WOMAC A pain index ($p = 0.0134$, $n = 6$). Of the subjects dosed with RTX providing voluntary long-term follow-up, three of four subjects who reached 1 year had maintained response. Side effects included post-procedural pain (100% in the RTX group vs 80% for placebo), nausea (43%), vomiting (17%), and headache (10%). Overall, the side effects were manageable and well tolerated [130]. This company subsequently reported positive topline results from a multicenter, phase IIa, randomized, dose-ranging, assessor-blinded, active and placebo-controlled, parallel-group prospective study evaluating the efficacy and safety of a single IA injection of various RTX doses compared with IA Zilretta (triamcinolone acetonide extended-release injectable suspension), or placebo for the treatment of pain due to moderate-to-severe OA knee pain (NCT04885972) [113]. The study met its primary and secondary objectives and demonstrated that RTX 20 µg is an effective pain treatment for longer durations (up to 1 year), with better score improvements at week 26 and 52 than the current standard of care (an active steroid injection, Zilretta) up to and past week 26 [113].

The second company that has a trial program for IA RTX in KOA has also reported long-lasting and significant analgesia following treatment of patients with chronic KOA joint pain with single IA doses of RTX [131]. In this open-label, phase Ib/IIa study, RTX had a favorable safety profile and was well tolerated. The majority of patients experienced substantial improvement in pain scores (as assessed by WOMAC and VAS), which were maintained over the 6-month follow-up period. Procedure-related pain was commonly reported, however, this was generally mild to moderate and transient [131]. A global phase III trials program has been initiated by this company for IA RTX in OA-related pain [132]. This program plans to include more than 1,800 patients across trial sites in Europe, the U.S.A., Latin America, South Africa, and Japan. At the time of writing, three phase III trials are ongoing: two randomized, placebo-controlled studies of single and repeated IA injections of RTX and one single-arm, open-label study of multiple IA injections of RTX (NCT05449132, NCT05248386, and NCT05377489, respectively). In the two placebo-controlled studies, the primary endpoint is change from baseline in WOMAC pain subscale score from baseline to week 12; the secondary endpoints being assessed from baseline up to week 52 in these studies also include the WOMAC pain subscale score. In the open-label study, the primary endpoint is the number of participants with treatment-emergent AEs from baseline up to week 78, and the secondary endpoints which are being assessed from baseline up to week 12 include the WOMAC pain subscale score.

5. Expert opinion

Current therapies providing pain relief for KOA are inadequate in terms of efficacy and are often associated with side-effects. In patients with end-stage KOA, TKA can result in pain relief and functional improvement [133]. The frequency of TKA is rising rapidly [134], particularly among middle-aged patients (up to 65 years old) [133]. However, TKA has an associated risk for serious AEs including thrombosis and infection [133], and around one-fifth of TKA recipients experience a suboptimal outcome (a good outcome being defined as patient-reported symptom improvement and satisfaction with results at 1-year post-TKA) [135]. This, together with the projected increase in worldwide prevalence for OA [136], means that there is a high need for novel approaches that provide durable pain relief and have a tolerability profile which is manageable and acceptable for patients and their healthcare professionals (HCPs).

In the structures of the knee joint, nociceptors are present in abundance, with a complex neuroanatomy [77]. Sensory afferent neurons are present and activated in many of the OA-involved joint tissues, such as the synovium, menisci, ligaments, and subchondral bone. Signals from these nociceptive fibers underpin a substantial component of the pain associated with KOA. In particular, TRPV1-expressing afferent neurons are key drivers of OA pain [137,136]. Precise and durable deactivation of pain signals originating from TRPV1-expressing nociceptors within the knee joint may hold potential to improve outcomes and quality of life in patients with KOA.

Topical capsaicin and zucapsaicin have provided proof-of-concept for using TRPV1 agonists to relieve pain symptoms in patients with KOA [114–116], however the topical formulation has drawbacks including uncertainty over whether sufficient concentration of drug can reach the target nociceptors in the knee, and the need for frequent reapplication. IA administration provides a more direct route of administration. As the effect of IA TRPV1 agonists on pain signaling is limited to TRPV1-expressing nociceptors in the knee, their use is not expected to alter signaling from the other (i.e. non-TRPV1-expressing) afferent neurones in the knee, or indeed from nociceptors outside of the knee joint. Furthermore, the IA route may also reduce the potential for drug–drug interactions, with other systemic analgesics or concomitant medications for comorbid conditions in people with KOA.

IA administration of TRPV1 agonists, such as RTX may therefore serve as direct-acting neuronal analgesics capable of selectively deactivating TRPV1-expressing nociceptors in the knee. For patients and their HCPs, targeting the TRPV1 pain pathway continues to show promise as a transformative approach to relieve pain associated with OA, which could avoid many of the limitations of current analgesic options. OA therapies that extend the time to TKA in KOA may also reduce healthcare costs [137], helping to alleviate surgery-related resource and capacity issues within healthcare systems. Long-term follow-up of KOA patients receiving novel TRPV1 agonists such as RTX could explore the impact of these treatments on disease-related pain, knee joint functionality and need for future TKA surgery.

Abbreviations

AE	Adverse event
AUC	Area under the curve
Ca^{2+}	Calcium ion
CCI	Chronic constriction injury
CGRP	Calcitonin-gene related peptide
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CS	Corticosteroid
CYP450	Cytochrome P450
DPN	Diabetic peripheral neuropathy
DRG	Dorsal root ganglion
EU	European Union
HA	Hyaluronic acid
IA	Intra-articular
IL-1	Interleukin-1
KOA	Knee osteoarthritis
LSMD	Least squares mean difference
mAb	Monoclonal antibody
MIA	Monoiodoacetate
MRI	Magnetic resonance imaging
Na^{+}	Sodium cation
NGF	Nerve growth factor
NIHR	National Institute for Health and Care Research
NPRS	Numeric pain rating scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OLE	Open label extension
PDPN	Painful diabetic peripheral neuropathy
PHN	Postherpetic neuralgia
PNS	Peripheral nervous system
RTX	Resiniferatoxin
siRNA	small interfering RNA
TKA	Total knee arthroplasty
TNF-α	Tumor necrosis factor-alpha
TrkA	Tropomyosin receptor kinase A
TRP	Transient receptor potential
TRPV1	Transient receptor potential vanilloid 1
US FDA	US Food and Drug Administration
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities arthritis index

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