Ion Channels and Osteoarthritic Pain:

Potential for Novel Analgesics

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Abstract

Osteoarthritis (OA) is a debilitating chronic condition widely prevalent in ageing populations. Whilst pathology includes cartilage erosion and joint re-modelling, patients experience great pain. Despite numerous studies, the details are frequently inseparable from other types of chronic pain and causes are unknown. Cartilage lacks afferent innervation in most circumstances, but other joint tissues contain nociceptive neurones. In addition to physical joint damage there is a strong element of joint inflammation. Genetic studies have identified several associations between ion channels and OA pain including $Na_V1.7$, P2X7 and TRPV1, however, several other channels are also implicated. Many ion channels involved with OA pain are common to those seen in inflammatory pain. This review considers causes of OA pain and discusses three possible pain-reducing strategies involving ion channel modulation: Chondroprotection, innate afferent nerve inhibition and inhibition of inflammatory hyperalgesia. A number of ion channels could be future targets for OA pain analgesia.

Introduction

Osteoarthritis (OA) is one of the most common causes of disability in the UK and the Royal College of Physicians estimates that 8.5m older people are affected in the UK alone[1]. When describing their symptoms at a relatively early stage of diagnosis, rheumatoid arthritis patients will often state that they have a debilitating stiffness, but OA patients will routinely present chronic pain. Pain arising from affected joints may occur spontaneously without direct activation from an external stimulus. One symptom of OA is mechanical hyperalgesia[2]; although pain is often experienced at rest too[3]. Other hallmarks of OA include formation of bone spurs (osteophytes), erosion of cartilage and inflammation of joint tissues. Ion channels are potential targets for OA analgesia since they are critical to formation of cartilage and inflammatory pain. Earlier this year the UK National Institute for Health and Care Excellence draft guidance on OA treatment cautioned against excessive use of a wide range of analgesics (including paracetamol/acetaminophen) and so the search for novel OA analgesics has become a research priority area. This review considers sources of OA pain including joint nociceptor ion channels and nociceptive primary afferent neurones. We will not discuss the complex topic of spinal and supra-spinal pain processing in detail, but these were reviewed recently by Zhang *et al*[4]. We explore the potential of ion channel modulating drugs and biologics to reduce pain and improve the quality of life – if not reduce disease progression.

Joint nociception.

Many joint afferent neurons are peptidergic (calcitonin gene related peptide (CGRP)/substance P (SP) expressing) C and Aδ sensory afferents[5-7], i.e. typical nociceptive nerves. Most parts of the joint receive nociceptive innervation; ligaments, meniscus, subchondral bone and synovium (Figure 1). Although cartilage is usually aneural, under certain circumstances, it does contain nociceptive neurones[8-9]. These could be a transient developmental stage before the tertiary structure of the joint is fully formed or the result of joint damage and remodelling, but clearly such neurones could initiate considerable pain. Aδ- and C-fibres innervating any or all joint tissues are likely to be activated during OA onset – whether this results from direct mechanical (bone-on-bone) activation, abnormal joint loading (e.g., excessive ligament stretch) or inflammation (e.g., in the synovium). It was once believed that there was no correlation between MRI analysis of joint degeneration and patient reported pain, but as MRI analysis increases in sophistication the discourse is progressively decreasing[10]. Recent studies show clear correlations between the presence of cartilage-denuded zones of subchondral bone in knee joints and pain severity[11].

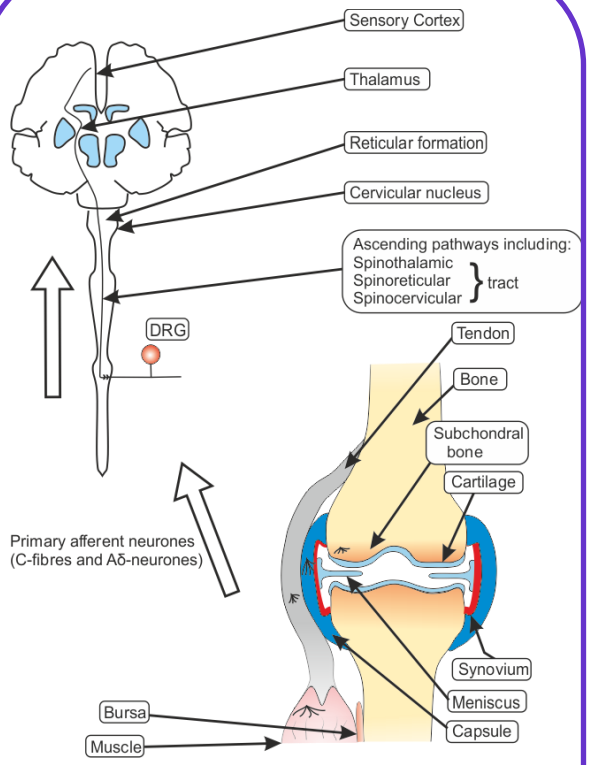

Figure 1: Innervation of a typical articular joint. Most tissues of the joint receive afferent innervations including C and Aδ neurones. These project to the dorsal Rexed laminae layers of the spinal cord, especially the substantia gelatinosa via dorsal root ganglia (DRG). In man, these afferent neurones typically synapse, then decussate and ascend contralaterally in the spinothalamic or spinoreticular tract. In non-primates the role of the spinothalamic tract is less clear and a greater proportion of nociceptive signal ascends via bilateral dorsal columns or spinoreticular tract[113]. Non primates also frequently have a considerable spinocervicular component of ascending neurones; in the cat and dog these are particularly important for sensory innervations of the nucleus proprius[114] along the length of the spinal cord. Conscious perception of pain

Joint tissue damage leads to local inflammation and sensitisation of neurones[12], but may also promote the formation of neuroma or ingrowth of nociceptive neurones, leaving scope for the generation of neuropathic pain. Currently, one of the greatest barriers in OA research is to establish the initial mechanism of pain generation. Afferent nociceptive neurones synapse first in the spinal cord dorsal horn, then ascend to the reticular formation or thalamus before finally reaching the somatosensory cortex (Figure 1). Potentially any step along this route, from chondrocyte to brain, could contribute to OA pain and is an attractive target for novel analgesics.

Ion channels in cartilage: "Chondroprotection".

Since there is now an established link between cartilage erosion and OA pain[11], a clear strategy for pain reduction would be to slow cartilage erosion or stimulate cartilage production. OA is associated with hypocellularity[13]; therefore it seems likely that a loss of chondrocytes contributes to disease progression[13]. Potentially chondroprotection will limit cartilage loss and thus reduce OA pain. Such chondroprotective drugs which could do this would be classed as disease modifying OA drugs [14]. The mechanism and sequence of events leading to the loss of cartilage are unknown; it is thought that it involves a loss of balance between extracellular matrix (ECM) synthesis, maintenance and destruction. This involves a range of matrix proteins and enzymes, many of which have been reviewed elsewhere[12, 15-17]. Gene wide association studies (GWAS) of OA demonstrate associations with a number of loci[18]. These genes mostly encode factors involved with chondrogenesis, endochondral ossification or apoptosis, rather than structural components of the ECM. Some of the genes identified are directly associated with channel activity including: TMEM30A; this is believed to encode a phospholipid channel or transporter-associated transmembrane protein[19], PTHLH/PTHrP; encodes parathyroid hormone-like hormone/hormone-related peptide and has been shown to inhibit voltage-gated calcium channel (VGCC) activity in neurones [20], RUNX2; a transcription factor which regulates chondrocyte pannexin channels[21] and, importantly, SMAD3; which inhibits transcription of an acid sensing ion channel (ASIC3) in chondrocyte-related nucleus pulposus (intervertebral disc) cells[22]. ASIC3 is strongly implicated in manifestation of OA pain (*see below*). Only five genes have been directly associated with OA pain [23]. Of these three were ion channels: SCN9A; encoding the voltage-gated sodium channel $Na_V1.7$. P2X7; a purinergic ligand-gated ion channel and TRPV1; the transient receptor potential channel vanilloid subtype 1. GWAS do not indicate where the associated gene fits into the progression of disease or the pain, but most of these channel families have been implicated in joint pharmacological experiments (discussed below). Alternatively, for a number of individuals, sudden joint impact may initiate a sequence of events leading to cell death, hypocellularity and subsequent cartilage erosion [24]. It has also been suggested that changes in osmotic environment (due to ageing or impact) could promote cell shrinkage and apoptosis[25]. Several ion channels are likely to be involved with this process including chloride[26] and potassium channels[27]; Kumagai *et al*[26] found the swelling-activated chloride ion channel to be central to this process. Inhibition of this channel could provide chondroprotection and would, ultimately, reduce pain. Pharmacological targeting of chloride channels is difficult because there are few sufficiently specific inhibitors and the molecular identity of the chondrocyte chloride channels is unknown. Recent bioinformatic analysis of the OA chondrocyte transcriptome identified differential expression of the TMEM16A chloride channels in OA chon-

drocytes[28]. Further ion channels could also be functionally changed in chondrocytes from OA subjects. For example, the ATP sensitive potassium channel (K_{ATP}) is expressed in chondrocytes[29] and appears functionally impaired in OA[30], although not apparently changed at the transcript level [28]. There are therefore several ion channels of chondrocytes which could be chondroprotectant targets, or indeed targets to halt the production of inflammatory mediators. These have been further discussed elsewhere[25, 28, 31-33].

Ion channels in innate primary nociceptive afferents.

Since the joint contains a number of nociceptive afferent neurones, it is likely that much of the pain of OA originates in the joint itself. One possible means of establishing this would be to inject local anaesthetics (LA). Typically, LAs work by inhibition of voltage-gated sodium channels, although lidocaine can also inhibit TRPA1 channels[34], which are important mediators of chronic pain (*see below*). Usage of LAs has the potential limitation that the synovium itself is a rather acidic tissue, and will be further acidified during inflammation. LAs are typically less effective in low pH[35] tissues since they are bases and only the charged form of the drug is inhibitory. Despite this limitation they can be effective in some patient cohorts with knee[36] and hip pain[37]. Nerve block itself, however, is frequently ineffective[38]. Current LAs are generally unsuitable for treatment of chronic joint pain, as the half-life of pain relief is too short and high doses of some LAs are chondrotoxic[39]. Until effective disease-modifying drugs are available, an alternative logical target is the primary afferent neurone. Cartilage erosion or abnormal joint loading could activate these neurones and create pain even in the absence of neuroplasticity, but broad evidence suggests that these neurones are hyperactive in a range of OA models[40]. Nociceptors are typically activated by chemical/ mechanical stimuli and/or noxious temperatures. Numerous studies have investigated which ion channels are present in joint primary afferents. VGCC, TRPV1, TRPV2 and P2X3 receptor-immunoreactive innervation have all been observed in rat joints[41-42]. Furthermore, TRPV1 has also been identified in both healthy and OA rat knee[43-44]. Mechanogated (stretch-activated) channels, sensitive to gadolinium and amiloride have also been found in a range of joint tissues including cartilage[33, 45] and small afferent C and Aδ neurones[46]. The identity of the stretch-activated ion channel present in joint afferent neurones is unknown, but one possible candidate is TRPV4, since it is present in afferents[47] and sensitive to mechanical stimulation[48]. Such stretch-activated channels have been identified in joints and are inhibited by hylan, which may be potentially useful therapeutically[49]. Besides targeting the ion channels themselves, block of conduction of nociceptive primary afferents is also a potential route to analgesia in OA, to which end the $Na_v1.8$

inhibitor (A-803467) has shown promising results reducing joint nociception to mechanical stimuli [50].

It is important to highlight a limitation in the understanding of OA pain; it is not known if there are any specific differences between nociceptive afferents innervating the joints and those innervating other peripheral tissues. This means that drugs for the treatment of joint pain will have a parallel affect on other nociceptive afferents within the body, or will have to be applied to just the affected area. Evidence suggests that topically applied anti-inflammatory drugs (e.g., diclofenac) can reach affected human synovial joints[51], however there is little data on off-target bioavailability. Off-target nociception is not ideal, but may not be highly problematic. It is critical that inhibitors of nociception do not inhibit other somatosensory afferents such as those conducting proprioception or kinaesthesia, since this could cause joint destabilization, accelerating the progression of OA, (see, for example, [52]). Since pain is itself a protective signal to animals, it is important to consider that, used in isolation, effective analgesia itself could result in patients overusing joints which still have the same structural damage.

Table I. Inflammatory mediators produced by chondrocytes.
Inflammatory mediators produced by chondrocytes, which have also been shown to modulate neuronal activity. Table modified from [12] with permission. Other references: NGF production in chondrocytes [115]. *Shown in joint tissue, but not shown to be produced by chondrocytes [75-76]. PGE2, prostaglandin E2

Direct sensitizers	Indirect sensitizers	Stimulators
Prostaglandin E2	Bradykinin*	ATP
Prostaglandin F2	Noradrenalin	Bradykinin*
Prostaglandin I2	Leukotriene B4	Histamine
ATP	Interleukin-1	Potassium
Bradykinin*	Interleukin-8	Proton
Proton	NGF-OP	PGE2
Tumor necrosis factor	Tumor necrosis factor	
Interleukin-6	Nitric oxide	
Substance P		

Inflammatory activation of ion channels in OA pain

OA can, in part, be distinguished from rheumatoid arthritis by the lack of systemic markers for inflammation; however, considerable evidence also links OA with joint inflammation. It has been suggested that OA may frequently result from biomechanical damage leading to chondrocyte driven inflammation and remodelling[12]. In addition to their role in cartilage production, chondrocytes have a direct role in inflammatory pain too, producing mediators which can both sensitise and activate neurones (Table I)[12, 53]. Pelletier *et al*[54]showed that chondrocytes obtained from OA patients actively produce nitric oxide (NO), prostaglandins, interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), IL-6, and IL-8. Inflammatory mediators are also produced by the synovial membrane and diffuse into cartilage. Here they manifest structural altera-

tions associated with OA disease progression[53]. Inflammatory mediators affect a range of ion channels, although it is unclear which channels and mediators are critical in OA pain. TNFα is one very strong candidate since anti-TNFα monoclonal antibody (adalimumab) produces a prolonged reduction of pain symptoms in an animal model[55]. TNFα has also been shown to directly modulate both VGCC and Na_V currents in DRG neurons, causing a decrease in VGCC conductance and an increase in Na_V[56]. Since gain of function of $Na_V1.8$ results in painful neuropathy[57], restricting the effects of TNFα could potentially reduce this Na_V-induced hyperalgesia. Several ion channels have been directly linked to these processes in joint inflammation and OA and are discussed below.

Sodium channels

The sodium voltage-gated family includes 9 sub-members $Na_V1.1$ to $Na_V1.9$; these are the principal channels involved with the upstroke of action potentials in nearly all mammalian neurones. The tetrodotoxin resistant $Na_V1.8$ is of particular relevance to analgesia, because it is most predominant in smaller C-fibre nociceptors. Epigenetic silencing of $Na_V1.8$ leads to hypoalgesia[58] and over activity would be expected to decrease pain thresholds[57]. A decrease in pain thresholds appears to be one of the effects of pro-inflammatory prostaglandins (whose receptors are heavily expressed in DRG and peripheral nerve fibres), which have been found in a number of studies to be involved in OA disease progression as well as being key mediators of pain. There are intriguing differences in the actions of the key prostaglandin E2 (PGE2) receptors in OA[59]. Activation of the prostaglandin EP2 and EP4 neuronal cell receptors stimulates pain and causes elevated levels of cyclic adenosine monophosphate (cAMP), whereas activation of EP3 is analgesic and causes decreases in cAMP[59]. Natura *et al*[59] showed that cAMP in primary afferents increases activity of $Na_V1.8/9$. Activation of the prostaglandin EP2 and EP4 neuronal cell receptors stimulates pain and causes elevated levels of cAMP, whereas activation of EP3 is analgesic and causes decreases in cAMP[59]. In addition to its beneficial effects for mechanically-induced pain, blocking the voltage-gated $Na_V1.8$ using antisense oligonucleotides has been shown to eliminate the generation of spontaneous activity in a CFA-induced model of chronic inflammatory pain[60]. As well as $Na_V1.8$ being of high importance in nociceptive transmission, Aδ-neurones are also central to this and therefore it would seem that $Na_V1.6$ is particularly important. Knock-down of $Na_V1.6$ reduced pain in a spinal inflammatory rat pain model, but left C-fibres largely unaffected[61]. Interestingly $Na_V1.7$, identified in the association studies[23] and upregulated in a CFA model of chronic inflammatory pain[62], has not been implicated in functional studies of afferent neurones, although characterisation of this channel is challenging due to a lack of selective pharmacological agents.

Acid sensing channels

While there are a number of pH sensitive ion channels, ASICs are the most strongly associated with OA. ASIC are a family of ion channels which preferentially conduct sodium and potassium ions. The inflammation of synovial tissue during progression of OA results in acidification which could result in change of activity of ion channels. Increased activity of acid sensitive ASIC or TRP channels could predispose neurones to excessive firing (and ultimately pain). ASIC are found in several joint tissues including chondrocytes themselves[63], where their block can reduce articular cartilage erosion in adjuvant-induced OA[64]. ASIC3 are found in joint primary afferents innervating synovial tissue and are increased in expression in MIA-induced OA[65-66]. Selective block of this channel by intra-articular administration of a peptide inhibitor (APETx2) reduced pain and inhibited disease progression[65]. A novel ASIC blocker, A-317567, has been reported to cause a reduction in hyperalgesia in models of inflammatory and post-operative pain[67]. However, there have been no clinical OA studies to date which describe the therapeutic benefit of ASIC inhibitors. It should be noted that a role for ASIC1a in chronic OA pain would be rather intriguing and not a simple activation of current by low pH, since ASIC channels, and ASIC1a in particular, are transiently active channels and desensitize after a few seconds of exposure to low pH[68].

Potassium channels

The potassium channel superfamily consists of over 70 subtypes and they are involved in several different levels of OA progression[31]. The classical two, four and six trans-membrane domain potassium channels (Kir1-7: Inward rectifiers, K2P: Tandem pore and K_V/K_{Ca}: Voltage-gated and calcium-activated potassium channels, respectively) are highly selective for potassium ions. Generally, potassium channels have a role in stabilizing the membrane potential or in action potential repolarization. As such, potassium channel modulation is a common physiological mechanism of changing the excitability of a neurone. In other cell types, such as chondrocytes and glial cells, potassium channels serve important roles in cell volume regulation, apoptosis and maintenance of potassium homeostasis[31]. There are a number of existing drugs used which currently target potassium channels in diseases such as diabetes, hypertension, epilepsy and angina [69], but none which are yet used clinically as analgesics. KiR3.x (GIRK), which couple to opioid receptors, could be one such target. Side effects of current centrally acting opioid drugs (somnia, euphoria, addiction etc.) limit their usefulness, but recently it has become clear that opioid receptors also mediate effective analgesia when applied peripherally[70]. Such μ-opioid agonists, could prove extremely useful analgesics for chronic pain conditions such as OA. So too could activation of the peripheral downstream apparatus of the μ-opioid receptor such as GIRK. In rats and humans, the peripheral analgesia of the inflammatory

neuropathic pain model is almost entirely dependent on GIRK[71]. This raises GIRK itself as a potential OA analgesia target. Interestingly, the work of Nockemann *et al*[71] found GIRK to be absent from mouse peripheral neurones in striking contrast to their human and rat counterparts. Another related and highly selective potassium channel implicated in inflammatory OA pain is the M-current potassium channel, or $K_V7.x$; this channel is activated by bradykinin in chronic inflammatory pain[72-73]. Bradykinin is strongly implicated in all kinds of inflammatory pain; some of its inflammatory actions are mediated by opioid receptors[74] and it can act synergistically with prostanoids further contributing to joint degeneration in OA[75]. Antagonists of the bradykinin B2 receptor have therefore been proposed to be potentially useful treatment agents for OA[76]. Bradykinin (along with the neurokinin-1 receptor) is also found to be over expressed in neurones in induced arthritis pain models[77-78] and a selective bradykinin receptor-2 antagonist (fasitibant) prevents the associated hyperalgesia[78]. BK directly sensitizes joint afferents[79] and BK antagonists have been used in the MIA model[80]. Future treatment options could also include targeting bradykinin's effector ion channels including GIRK, calcium-activated chloride channels[72-73] and TRPV1 (*see below*).

There are a number of cation channels which express weaker selectivity for potassium, such as the hyperpolarization-activated cyclic nucleotide gated (HCN) channels[81]. HCN channels are a relatively small subfamily of ion channels (HCN1 to HCN4) that are closely related to the other cyclic nucleotide gated (CNG) channels. Often classified as non-selective, they actually have a K^+ to Na^+ selectivity ratio of approximately 5:1 and are thus weakly selective potassium channels[81]. HCN channels can be activated by cGMP (and cAMP) although the mechanism involves shifts in their voltage activation sensitivity. HCN channels are expressed in neurones innervating the rat temporomandibular joint and contribute to inflammation-induced mechano-hypersensitivity where ZD7288 (a selective HCN blocker) exhibits profound anti-mechanical hypersensitivity activity[82]. The expression of these channels in both cardiac and sensory tissues may limit the translation of these drugs to clinical trials unless they can be shown to discriminate between the two tissues with high selectivity.

Transient Receptor Potential (TRP) Channels and Calcium Channels

TRP ion channels are emerging as widely expressed molecular sensors in the musculoskeletal system [48, 83]. Most of these channels have significant permeability for calcium ions, and some are highly selective for calcium. TRP channels are important, not just to the function of chondrocytes[25, 45], but also in the progression of OA pain. For example, in addition to activating potassium channels, bradykinin also contributes to joint pain by activating a range of TRP channels such as TRPV1[84-85], TRPV4 and TRPA1[86-87]. TRPV1 and TRPV4 are also activated by protease activated receptor (PAR-

2), another inflammatory receptor with particular relevance to OA; PAR-2 couples to TRPV1/4, stimulates pain and exacerbates OA progression[47, 88]. Furthermore TRPV1 is up-regulated in joint primary afferent neurons the MIA model of OA[44] and TRPV1 KO decreases pain responses to both chemical and thermal stimuli of mouse paw[89]. These channels have also been identified in mouse ankle and knee [90]. Further interest has surrounded potential inhibition of TRPV1 in OA chronic pain since Chapman and colleagues show an association with the Ile585Val TRPV1 variant is involved in risk of painful knee OA[91]. Application of the TRPV1 inhibitor A-889425 did decrease afferent nerve activity in CFA-hyperalgesia rats[92] and A-995662 (another TRPV1 antagonist) successfully reduced MIA induced changes in grip force, but in contrast the alternative TRPV1 inhibitor AMG9810 did not appear to reduce OA pain[93]. The potential benefits of selective TRPV1 drugs are enormous, but have yet to be realised due to potential side effects. It should be said however, that the total selectivity of any novel inhibitors such as A889425 and AMG-9810 takes many years to establish. In this particular case, the two compounds are chemically rather different; being a trifluoromethylsulfonyl-phenyl and a 1,4-benzodioxine respectively. Encouragingly, antisense knockdown of the closely related TRPA1 channel also reduces pain in a model of neuropathic pain[94], however, systemic TRPA1 inhibition (A-967079 or HC030031) is ineffective in reversal of CFA-hyperalgesia or MIA-induced joint pain [93, 95].

Cannabinoids (CB) have been extensively studied as potential modulators of chronic pain. Reports of their efficacy for OA pain have been conflicting, with promising data emerging from animal models[96-97], but less promising data resulting from clinical trials[98]. Some of this divergence may result from currently unknown differences in ion channels between species, as discussed for GIRK above[71], but other issues may involve the rather complex actions of cannabinoids on CB receptors and TRP channels. For example, CB2 receptors are co-localized with TRPV1 receptors in DRG and the selective agonist GW405833 appears to decrease afferent nerve firing in control knees, but increase nociceptive firing in MIA-treated OA rat knees[99]. The latter effect appears to involve TRPV1, possibly through a CB2-TRPV1 positive coupling. The TRP family contains dozens of submembers however, and it is likely that other members also play a role in OA pain, for example, TRPM3 is expressed in DRGs and trigeminal ganglia sensory neurones, is activated by heat and it has been shown that $TRPM3^{-/-}$ mice have impaired sensation of noxious heat and thermal hyperalgesia [100].

VGCC are important for Ca^{2+} entry in most neurotransmission and are one of the targets of CNS endorphins and enkephalins (and their exogenous counterparts, the opioids, e.g., morphine). Unsurprisingly, therefore, VGCC are also involved with chronic and neuropathic pain[101]. In

particular, the α_{2d-1} subunit of VGCC is increased in MIA-induced OA and thus contributes to the generation of pain[102]. A number of VGCC blockers are available and one in particular, gabapentin, is of potential benefit for treatment of OA pain[103]. Interestingly, gabapentin appears to be only in use by a very small cohort of OA patients[104]. Store-operated calcium channel inhibitors have also been recently implicated as potential analgesics for chronic inflammatory pain [105].

Purinergic channels

The purinergic membrane receptor super-family is classed into P1 and P2 receptor families of which the P2 family are of particular relevance to OA pain. These are activated by extracellular nucleotides (ATP or ADP). P2X are ligand-gated ion channel receptors (P2X1-7), whereas P2Y are G-protein coupled receptors. Several members of this family have been identified in cartilage including; P2X2, P2X3, P2X4 and P2X7[106-107]. It has been shown that P2 receptor signalling is altered in OA[108] with elevated levels of ATP inducing desensitisation of purinergic membrane receptors. In terms of the OA pain pathway, P2X receptors have also been identified in peripheral glial cells and play a role in neuropathic pain[109]. Glial cells (peripheral and spinal) are non-excitable cells in the nervous system and express a large range of ion channels and receptors which are likely to contribute to the onset of neuropathic-type pain including a component of OA[109-110]. Glial cells produce a variety of proinflammatory mediators, including IL-1β, TNF-α, and NO. Following peripheral nerve damage, P2X4 receptor upregulation in spinal microglia cells and P2X7 upregulation in macrophages has been reported[3]. Human studies have also shown that both the P2X7 and microglial cell expression has increased following chronic pain[3]. This channel plays a part in the initiation of neuroinflammation[111] and recent studies have developed a novel P2X7 antagonist, JNJ-47965567[112], which could be of potential benefit as an OA pain analgesic. Whilst it exerted only modest analgesia in a rat spinal lesion model of neuropathic pain[112], it is highly selective and readily penetrates the CNS and so could potentially act at any point along the ascending OA pain pathway.

Conclusions

In many ways OA typifies chronic pain with remodelling of joints, plasticity of innervation and afferent nociceptive pathways. However, unlike idiopathic chronic pain, there are also established nociceptive mechanisms involving ion channels in joints and primary afferent neurones. There is little specific evidence to class OA as a channelopathy as such, but clear evidence suggests that both pain generation and cartilage degeneration involve ion channels. Numerous studies discussed in this review also highlight the coupling between joint degeneration, inflammation and nociception in ac-

counter-intuitive direction. Targeting these ion channels is therefore a highly important objective for those developing treatments for OA pain.

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