Emerging Targets for the Management of Osteoarthritis Pain

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Abstract

Worldwide, osteoarthritis (OA) is one of the leading causes of chronic pain, for which adequate relief is not available. Ongoing peripheral input from the affected joint is a major factor in OA-associated pain. Therefore, this review focuses predominantly on peripheral targets emerging in the preclinical and clinical arena. Nerve growth factor is the most advanced of these targets, and its blockade has shown tremendous promise in clinical trials in knee OA. A number of different types of ion channels, including voltage-gated sodium channels and calcium channels, transient receptor potential channels and acid-sensing ion channels, are important for neuronal excitability and play a role in pain genesis. Few channel blockers have been tested in preclinical models of OA, with varying results. Finally, we discuss some examples of G-protein coupled receptors, which may offer attractive therapeutic strategies for OA pain, including receptors for bradykinin, calcitonin gene-related peptide, and chemokines. Since many of the pathways described above can be selectively and potently targeted, they offer an exciting opportunity for pain management in OA, either systemically or locally.

Keywords

Osteoarthritis; Pain; Targets; Ion channels; Nerve Growth Factor; GPCRs

Introduction

Osteoarthritis (OA) is a painful disease of synovial joints that results in failure of the joint as an organ [1]. It is by far the most common form of arthritis and pain associated with OA is quickly becoming one of the leading causes of chronic pain in the world [2]. This is because

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the prevalence of this chronic joint disease is increasing as the population ages and adequate treatments are not available [3, 4].

Chronic pain associated with OA can be generated, modified, and maintained at different levels along the neuraxis, all of which may provide opportunity for pharmacological intervention [5, 6]. There is ample clinical evidence to indicate that ongoing peripheral input from the affected joint drives OA pain. Firstly, intra-articularly administered local anesthetics alleviate knee pain [7]. Further, recent clinical trials with antibodies that neutralize the peripherally acting pain mediator, nerve growth factor (NGF), have shown promising analgesic efficacy [8]. Finally, in the majority of cases, total joint replacement results in pain relief [4]. Therefore, the focus of this narrative review is on peripheral mechanisms of pain, in particular nociceptor activation and sensitization. We will discuss emerging targets that show promise in preclinical models of OA and/or in clinical trials.

Peripheral mechanisms of pain

Acute pain is a normal physiological response to a potentially harmful event resulting in the avoidance of tissue damage. The neuronal substrates for pain include a variety of pathways such as the dorsal root ganglion and trigeminal sensory neurons in the periphery as well as central pathways linking the dorsal horn of the spinal cord to higher centers of consciousness [9]. Under some circumstances, including tissue damage and infection, plastic changes in pain pathways produce abnormal excitability and pain in the absence of normal stimulation. Small fiber neuropathies associated with numerous systemic disorders including diabetes mellitus, hyperlipidemia, amyloidosis, Fabry syndrome, celiac disease, sarcoidosis, and human immunodeficiency virus infection affect small non-myelinated C-fibers and lightly myelinated A□-fibers and present with pain and autonomic symptoms.

Tissue damage and inflammation result in release of a wide array of mediators that can bind specific receptors on nociceptors that innervate the affected tissues, resulting in different biological effects, including: neuronal excitation, eliciting pain; peripheral sensitization; and release of neuropeptides such as substance P and calcitonin-gene related peptide (CGRP), which contribute to neurogenic inflammation (Fig. 1). Excessive neuronal activity of primary sensory neurons can also trigger neuroinflammation, which is characterized by activation of satellite glial cells and infiltration by immune cells such as macrophages in the dorsal root ganglia (DRG), where the cell bodies of the sensory neurons reside [10, 11].

The pathways outlined above (Fig. 1) indicate that a broad array of peripheral targets is potentially "druggable" with the aim of achieving relief of joint pain. However, few of these have been studied specifically in the context of experimental models of OA-related pain, and very few have been assessed in clinical trials in OA patients. Below, we will discuss a selection of novel peripheral targets that are emerging in the preclinical and clinical arena.

1. BLOCKADE OF NERVE GROWTH FACTOR ACTIVITY

Inhibition of NGF activity has been explored as a powerful strategy for pain management in OA. NGF is a member of the neurotrophin family, proteins that are critical to the development and maintenance of the nervous system. In addition, NGF is a pro-algesic

molecule that contributes to peripheral nociceptor sensitization [12]. Experimental evidence for a pivotal role for NGF in OA joint pain is steadily increasing. Expression of NGF in the inflamed synovium of knee OA patients is associated with the presence of pain [13]. Other joint tissues can also produce NGF: many years ago, it was shown that human chondrocytes produce NGF and express its high affinity receptor, TrkA, and that these molecules are upregulated in OA [14]. Renewed interest in the contribution of NGF to joint pain led to several recent reports that stimuli present in the OA joint may promote production of NGF by chondrocytes, including interleukin (IL)-1β, the adipokine visfatin [15], transforming growth factor (TGF)β [16], as well as mechanical injury in murine cartilage [17]. Therefore, OA cartilage - though aneural -may provide a rich source of NGF and thus locally contribute to pain generation. In two rat OA models, meniscal transection and mono-iodoacetate (MIA)-induced OA, it was shown that pain responses to NGF locally administered into the knee cavity are increased in OA compared to non-OA joints [18], indicating that local production of NGF may be crucial for the generation of pain. In the rat MIA model, a single dose of anti-NGF antibody exerted a long-lasting beneficial effect on pain during motion, as assessed by monitoring gait [19]. A soluble NGF receptor fragment containing the NGF binding domain, TrkAd5, had a beneficial effect on weightbearing deficits 16 weeks after destabilization of the medial meniscus (DMM) in the mouse [20]. A recent clinical trial in dogs with degenerative joint disease suffering from chronic pain demonstrated a clear analgesic effect of an anti-NGF antibody [21].

There are different strategies for reducing NGF activity [22], including monoclonal antibodies that bind and sequester free NGF as well as small molecules that block its high-affinity receptor, TrkA. Initial clinical trials with monoclonal anti-NGF antibodies in knee OA patients were very encouraging but abruptly halted in 2010 after reports of unexpected accelerated joint destruction leading to total joint replacement, especially in subjects where anti-NGF antibodies were combined with non steroidal anti-inflammatory drugs (NSAIDs). Trials have now resumed (reviewed in [8]). Selective small molecule inhibitors of TrkA are in development and their analgesic efficacy has been demonstrated in preclinical models of OA [23, 24]. A first-in-human study with ascending single intra-articular doses of the TrkA inhibitor, GZ389988, in patients with painful osteoarthritis of the knee has recently commenced (https://clinicaltrials.gov/ct2/show/NCT02424942?term=trka+and +osteoarthritis&rank=1).

2. ION CHANNELS

DRG neurons that mediate pain signaling under physiological conditions express a number of different types of ion channels that can enhance neuronal excitability (Fig. 1). Electrogenesis in DRG and trigeminal neurons is dependent on the activity of a variety of voltage-dependent ion channels, including voltage-gated sodium and calcium channels (VGSC and VGCC). Changes in the properties of these channels may drive hyperexcitability in a variety of chronic pain states and so they are widely believed to be suitable drug targets for the treatment of chronic pain conditions.

2.1. Voltage-gated sodium channels (VGSC)

VGSCs are responsible for the upstroke of the action potential as well as other features that have important effects on neuronal excitability. The molecules that form the pore of these channels are large multidomain proteins with molecular weights of around 270 kDa. VGSCs in mammalian cells consist of a gene family encoding 9 different proteins which exhibit an approximately 50% sequence homology. The action potential in DRG neurons is particularly dependent on $Na_V1.3$, $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$. These channels are all found in non-myelinated and thinly myelinated DRG neurons, populations that have been traditionally associated with pain. $Na_V1.7$ channels are also found in sympathetic neurons. $Na_V1.3$ is normally expressed in embryos but can also be upregulated in DRG neurons in response to tissue damage. Both $Na_V1.3$ and $Na_V1.7$ are blocked by the classic sodium channel blocker, tetrodotoxin, whereas $Na_V1.8$ and $Na_V1.9$ are resistant to this toxin (reviewed in [25, 26]. The role of these channels in the genesis of pain has been particularly indicated through several mutations recently detected in the human population. For example, loss of function mutations in SCN9A, the gene encoding $Na_V 1.7$, results in dramatic reductions in pain sensation in the few families that are known to have survived with these types of mutations [27]. Dominant gain-of-function mutations in SCN9A were first described in two severe pain syndromes, inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD) [28, 29] both of which are autosomal dominant. These observations have encouraged the idea that small molecule $Na_V1.7$ blockers may be effective treatments for pain. The mechanism of action of these substances, however, may not be completely clear as it has also been recently demonstrated that strong antagonism of $Na_V1.7$ activity leads to strongly increased expression of opioid peptide levels, which may contribute to the analgesic effects of loss of $Na_V1.7$ function. Whatever their precise mechanism, several of these substances have entered the drug development pipeline (for recent review, see [30]).

In the context of OA, one study reported a single nucleotide polymorphism (SNP) in SCN9A that was correlated with increased pain sensitivity in OA patients [31], but this could not be replicated in larger cohorts [32]. However, because several different types of sodium channels contribute to nociceptor electrogenesis, blockers of several of these might be useful therapeutically in OA pain. In preclinical models, the effect of selective blockade of either $Na_V1.7$ or $Na_V1.8$ has been explored. In rat MIA, a selective blocker of $Na_V1.8$ significantly reduced the firing rate of joint afferents during noxious rotation of the joint but had no effect during non-noxious rotation, while injecting the compound into the knee cavity attenuated hindlimb incapacitance and secondary allodynia [33]. ProTxII, a tarantula toxin that potently and selective inhibits $Na_V1.7$ channels, or the selective $Na_V1.8$ blocker, A-803467, inhibited neuronal responses evoked by both low-threshold and suprathreshold stimuli in MIA but not control rats, indicating that these channels contribute to arthritic pain [34]. The role of sodium channels in OA pain is also supported by the observation that lacosamide, an anticonvulsant drug that acts as a state-dependent sodium channel blocker, reduced hypersensitivity to mechanical stimuli in the same model, although it failed to correct weightbearing deficits [35]. Information on the effect of selective blockade of VGSC in more translational models of OA [36] is not yet available, but can be expected to provide very useful information with respect to the specific relative contribution of these channels to OA-related pain.

2.2. Voltage-gated calcium channels (VGCC)

In addition to VGSCs, voltage-sensitive calcium channels (VGCCs) may also be targets for OA pain. N-type calcium channels ($Ca_V2.2$) are known to be the major route for Ca^{2+} entry into the nerve terminals of nociceptors. Therefore, blockers of these channels would be expected to produce antinociceptive effects by reducing transmitter release. For example, ziconitide, a peptide $Ca_V2.2$ blocker obtained from a Cone snail, has been shown to be effective in several chronic pain conditions [37]. It has been suggested that VGCCs are important for mechanical excitability of slowly conducting afferents innervating the rat knee [38]. Spinal or systemic administration of the Ca_V2 channel blocker, N-triazole oxindole (TROX-1), significantly reduced neuronal measures of nociception in the rat MIA model [39].

There has also been wide interest in the use of gabapentinoids such as gabapentin and pregabalin in the treatment of chronic pain conditions, including OA. It is most likely that the beneficial effects of these molecules are due to their binding to the α2δ non-pore forming subunit of VGCCs. Hence, both VGCCs in the DRG and the central and peripheral terminals of nociceptors may be targeted by gabapentinoids. Both gabapentin and pregabalin have also been shown to have beneficial effects in the rat MIA model [40] and in surgical models in rats and mice [41, 42].

2.3. Transient Receptor Potential Channels (TRP)

Transient Receptor Potential (TRP) channels are a superfamily of non-selective cation channels widely distributed throughout the body. These channels can be activated by a variety of animal and plant substances that produce pain and other sensory effects. These include the well-known effects of the hot pepper-derived molecule, capsaicin (TRPV1), the cooling substances menthol and eucalyptus (TRPM8) and several irritants such as wasabi and mustard oil (TRPA1) (for review, see [43]). Members of the TRP vanniloid (TRPV) family, TRPV1 in particular, are highly expressed in nociceptive neurons and can be activated by noxious stimuli either directly (temperature, protons) or indirectly through transactivation by activation of receptors such as TrkA (NGF) or diverse G-protein coupled receptors (GPCRs) (bradykinin, prostanoids, chemokines) (Fig. 1). Not only are these channels involved in physiological pain responses but their phosphorylation and other modifications results in sensitization in diverse chronic pain conditions. The role of TRPVI has been investigated in particular and, following its discovery [44], numerous small molecule antagonists or desensitizing agonists were produced with the expectation that they would be therapeutically effective. Unfortunately, their clinical development has been restricted due to a variety of side effects such as hyperthermia that were rapidly apparent [45]. Nevertheless, the important roles that these channels play in pain physiology has encouraged the view that they should still be considered potential targets for pain conditions including OA [46]. A second generation of TRP channel modulators is now under development with the aim of trying to divest these molecules of their side effects.

TRPV1 has been implicated in genetic susceptibility to symptomatic knee OA [47]. Human OA synovium displays increased TRPV1 immunoreactivity and both local and systemic administration of the selective TRPV1 receptor antagonist, JNJ-17203212, reversed

sensitization of joint afferents and inhibited weight-bearing asymmetry in the rat MIA model of OA pain [48].

TRPV1 can also be targeted by channel agonists, such as capsaicin and the potent vanilloid analogue, resiniferatoxin, which cause an initial burning pain followed by a desensitization of the primary afferents. Topical capsaicin derivatives (creams) are used in OA (reviewed in [49]), and compounds for intra-articular administration are in development (https://clinicaltrials.gov/ct2/show/NCT02558439).

Interestingly, it was recently reported that TRPV1 channels are molecular targets of hyaluronan (HA) [50], which is used intra-articularly in knee OA and reportedly provides analgesia. In this study, HA reduced excitability of TRPV1 channels, which may be exploited to optimize its analgesic properties.

2.4 Acid Sensing Ion Channels (ASIC)

ASIC channels are a group of amiloride sensitive non-specific voltage insensitive cation channels that are activated by extracellular protons. Each channel represents a homo or heterotrimer formed from a family of six ASIC protein subunits. ASIC channels are found in both neuronal and non-neuronal tissues and are highly expressed in small nociceptive DRG neurons. Activation of ASIC channels in these neurons produces an excitatory depolarizing current and hypersensitive pain behavior (reviewed in [51]). The potential role of ASIC channels in pain physiology is illustrated by the effects of a number of toxins. For example, toxins from the venom of the Texas coral snake strongly activated ASIC channels in DRG neurons accompanied by intense pain [52]. On the other hand, toxins isolated from the venom of the black mamba (mambalgins) blocked pain behavior in a variety of experimental paradigms (formalin test, carrageenan etc). In some tests the effects of mambalgins approached those produced by morphine [53].

In rats, repeated injections of acidic saline into the knee joint cavity induced weight-bearing asymmetry and decreased knee compression and paw withdrawal threshold. This appeared to be mediated through ASIC3, since a selective ASIC3 antagonist (but not ASIC1 or TRPV blockers) reduced the observed hyperalgesia [54]. ASIC channels are targeted by a number of other toxins from a wide variety of species. In rat MIA, daily intra-articular administration of APETx2, a 42-amino acid toxin component from the venom of the sea anemone Anthopleura elegantissima [55], reduced pain-related behavior and secondary hyperalgesia [56]. Similar effects were produced by the non-specific ASIC blocker amiloride.

3. G-PROTEIN COUPLED RECEPTORS (GPCRs)

The human genome codes for some 800 GPCRs, representing about 4% of the genome. GPCRs are well represented in all of the cells that constitute the peripheral and central components of the pain pathway. GPCRs have proved to be highly "druggable" targets in the past [57]. Depending on the G-protein involved in signaling, GPCRs may have excitatory or inhibitory effects on pain neurons. Examples of the influence of GPCRs on pain are the pro-algesic effects of bradykinin and the analgesic effects of morphine. In some instances,

important GPCRs are expressed directly by nociceptive neurons and in other instances by cells in direct communication with these neurons. In either case, the pro- or analgesic effects of activating different GPCRs may offer attractive therapeutic strategies depending on their role in OA. Major examples are discussed below.

3.1 Bradykinin Receptors

Kinins such as bradykinin (BK) and Lys-BK are peptides involved in both acute and chronic inflammation. They induce prostaglandin synthesis and contribute to symptoms that include pain, vasodilation, and edema, indicating a putative role for kinins at several levels of OA pathology [58]. There are at least two kinin receptors, B1 and B2, which belong to the Class I of GPCRs. B1 receptors mediate the effects of C-terminal des-Arg kinin metabolites, while B2 receptors mediate the effect of BK and Lys-BK. It appears that B2 receptors are expressed not only on knee nociceptors but also on synoviocytes and chondrocytes [58]. BK has been shown to evoke release of prostaglandin E2 and maybe CGRP in knee joint preparations of STR/N1 mice, which spontaneously develop OA [59]. Observations such as these have encouraged the view that B2 antagonists might be therapeutically useful in OA. The synthetic decapeptide, Icatibant, is a potent, stable, specific, and long acting antagonist of the B2 receptor while Fasitibant is a small-molecule B2 receptor antagonist. Results of clinical trials with intra-articular injection of these inhibitors in subjects with painful knee OA have been encouraging [60, 61] and a large randomized placebo-controlled trial was recently completed (https://clinicaltrials.gov/ct2/show/study/NCT02205814)

3.2 CGRP and Substance P Receptors

Nerves containing the peptide neurotransmitter CGRP have been widely implicated in a number of pain scenarios. In particular the peripheral terminals of CGRP-containing DRG nociceptors innervate several structures in the knee and show alterations in their pattern of innervation in OA [62, 63]. Release of CGRP from the peripheral terminals of nociceptors is thought to play an important role in the genesis of neurogenic inflammation and other pain-associated phenomena. For example, the vasodilation of cerebral blood vessels observed in association with migraine is thought to be a consequence of CGRP release and antagonism of the action of CGRP by small molecule receptor antagonists or antibodies to CGRP itself is currently a promising therapy for migraine [64]. CGRP release has been observed in the joints of OA affected rodents and CGRP receptors are expressed by different joint tissues. In rat models of OA (MIA and MMT), a role for CGRP in peripheral sensitization has been demonstrated [65]. Such observations have indicated that drugs or antibodies that antagonize the effects of CGRP may be useful in counteracting the effects of this peptide in OA. Indeed, a newly developed antibody against CGRP had a potent and prolonged analgesic effect in preclinical models, as measured by weight-bearing asymmetry [66].

In addition to CGRP, it is well established that neuropeptides of the tachykinin family, particularly substance P and neurokinin A, are also localized in a large number of nociceptors and it is thought that release of these peptides in the dorsal horn and from peripheral terminals can produce pain and neurogenic inflammation, respectively. The tachykinin receptor, NK_1R, is expressed by neurons in the dorsal horn and tachykinins can be released from central terminals of nociceptors. Tachykinin receptors are also expressed

peripherally on blood vessels and a variety of immune cells. These data have encouraged the idea that NK_1R antagonists might be effective interventions in pain. However, although several small molecule NK_1R antagonists have shown promise in preclinical studies they are yet to show clinical effectiveness in humans, including patients with osteoarthritis pain [67, 68].

Finally, there are numerous other neuropeptides associated with DRG neurons (*e.g.*, VIP, NPY, galanin). Here again, in preclinical studies these substances can be shown to modulate pain related behaviors but the therapeutic potential of drugs that block receptors for these neuropeptides in OA pain remains to be established.

3.3 Chemokine Receptors

Chemokines are a family of small, secreted proteins that have been shown to play a fundamental role in leukocyte chemotaxis and tissue/stem cell development. Several investigations noted the expression of chemokine receptors in the nervous system including DRG nociceptors [69] and the CXCR4 receptor was shown to be responsible for guiding the migration of DRG progenitors from the neural crest during development [70]. In the adult, the expression of several chemokines and their receptors was shown to be upregulated in the DRG in association with the development of chronic pain. Electrophysiological studies demonstrated that activation of chemokine receptors expressed in the DRG had a potent excitatory effect, indicating that chemokine signaling may play an important role in the genesis of hyperexcitability in chronic pain [69].

Although the expression of several chemokine receptors by DRG neurons has been demonstrated, particular attention has been centered on the role of the chemokine, monocyte chemoattractant protein (MCP)-1 (CCL2), and its receptor, CCR2. CCR2 antagonists and knock out of the *Ccr2* gene protected mice from pain hypersensitivity in a number of mouse models [71, 72]. In a surgical mouse model of OA, CCL2/CCR2 were found to be highly expressed in DRG neurons and *Ccr2* null mice showed an abbreviated pain phenotype, while a CCR2 antagonist was also able to ameliorate pain behaviors [73]. Hence, it has been suggested that chemokine receptor antagonists, and CCR2 antagonists in particular, may be a novel therapeutic intervention in OA. CCR2 antagonism has been viewed as a promising drug mechanism in OA and several specific CCR2 antagonists are undergoing clinical trials. However, no positive data have been forthcoming to date.

3.4 Proteinase-activated receptors (PARs)

PARs constitute a unique family of GPCRs that are widely expressed, including on sensory neurons. Signaling through PARs requires serine-protease-mediated proteolytic cleavage of the extracellular domain, which reveals a new N-terminus that then acts as the ligand for the receptor. Evidence is increasing that PARs play a role in inflammatory pain, including arthritis pain (reviewed in [74]). PAR2 is expressed in DRG neurons that innervate the rat knee, and its activation resulted in joint nociceptor firing rate during non-noxious and noxious rotation of the knee [75]. Different strategies to target these receptors for pain relief are being explored, with many examples in preclinical models [74]. For instance, selective

blockade of PAR4 inhibited PAR4-ligand-induced firing of joint nociceptors in rats [76]. However, data in experimental or clinical OA pain are not yet in the public domain.

4. OTHER TARGETS

Naturally, these are not the only potential targets for novel therapeutic interventions in the periphery. For example, botulinum neurotoxins A1 and B1 can alter nociceptive processing when administered locally into joints, and there is great interest in their potential application for OA pain (reviewed in [77]). Manipulation of the cannabinoid system is also heavily studied as an approach for OA pain management [78]. Efforts have been made to produce agents that only activate CB1 cannabinoid receptors peripherally and so are free of any psychotropic effects. Finally, several inflammatory cytokines are elevated in the OA joint, and these cytokines may well contribute to sensitization of sensory nerves innervating the joint, and thus to pain (for a detailed review, see [79]). Clinical trials up to date have had mixed results. Monoclonal antibodies against TNF-α had an analgesic effect in a small open-label trial in symptomatic knee OA with joint effusion [80], but were not efficacious in a randomized, placebo-controlled trial in patients with hand OA who were unresponsive to analgesics and NSAIDs [81]. Intra-articular administration of the IL-1 receptor antagonist, anakinra, was not efficacious in a multicenter, randomized, double-blind, placebo-controlled study in patients with symptomatic radiographic knee [82]. A phase2 double-blind placebo controlled trial in symptomatic knee OA with effusion is currently in progress, testing the effect of a dual variable domain immunoglobulin molecule that specifically and potently neutralizes both IL-1α and IL-1β [83].

Conclusions

Clearly, the abundance of peripheral targets that are potentially expressed on nociceptors in the joint (Fig. 1) begs the question as to how they each contribute to sensitization and pain in the course of OA. It seems that future research should be directed toward carefully documenting the localization of these targets in the OA joint and their contribution to pain, as well as elucidating how these different pathways integrate into networks that drive OA joint pain. Since many of the pathways described above can be selectively and potently targeted, they offer an exciting opportunity for analgesic drug development. However, it should be realized that OA is a multifactorial chronic disease, and human brain imaging studies are increasingly uncovering the complex networks of sensory and emotional experiences that underlie chronic pain [84]. Therefore, a final description of OA pain will presumably involve integration of peripheral and central components at all levels of the neuraxis.

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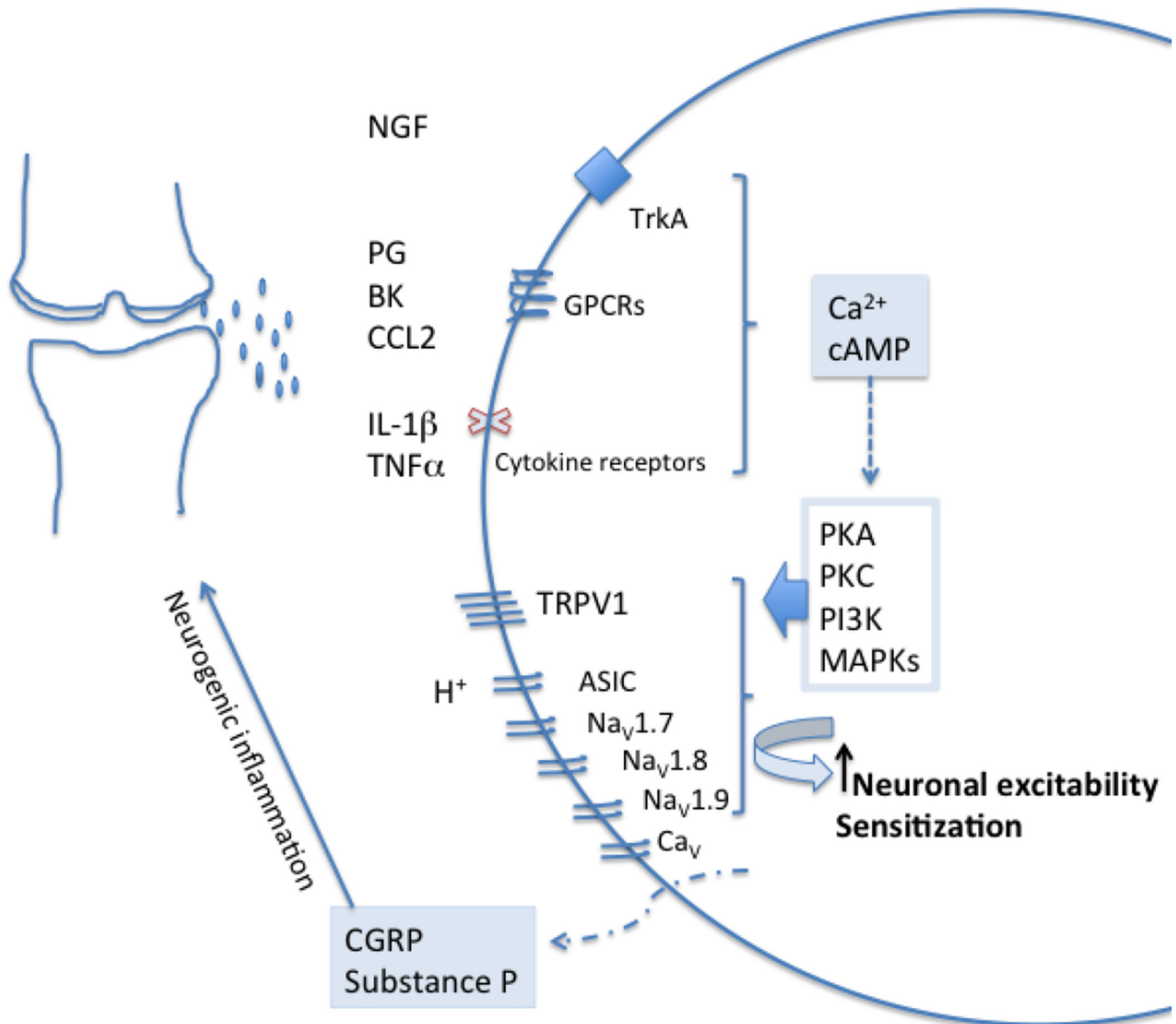
Fig. 1.
Inflammatory mediators present in the OA joint include prostaglandins, bradykinin, H^+,
nerve growth factor (NGF), pro-inflammatory cytokines (TNF-α, IL-1β), and pro-
inflammatory chemokines such as CCL2. Receptors for all these mediators, including
GPCRs, tyrosine kinase receptors, and cytokine receptors, are present on nociceptors. Their
activation results in the generation of second messengers such as Ca^{2+} and cAMP, which in
turn activates several kinases, such as the PKA, PKC, CaMK, PI3K, and MAPKs (ERK,
p38, and JNK). This modulates key ion channels, such as transient receptor potential ion
channel V1 (TRPV1) and voltage-gated sodium-channels, $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$,
causing hypersensitivity and hyperexcitability of nociceptors. This process is known as
peripheral sensitization. Nociceptor activation also results in the release of the

neuropeptides, substance P and CGRP, which cause vasodilation and neurogenic inflammation (adapted from [11]).