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Review

Voltage gated sodium and calcium channel blockers for the treatment of chronic inflammatory pain

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HIGHLIGHTS

- Voltage gated sodium and calcium channels have major role in inflammatory pain.
- Chronic inflammatory pain may progress to encompass neuropathic pain.
- Therapeutic potential of sodium and calcium channel blockers for inflammatory pain.
- Selective $Na_V1.7$,1.8, N- and T-type blockers may improve chronic pain treatment.

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ABSTRACT

The inflammatory response is a natural response of the body that occurs immediately following tissue damage, which may be due to injury, infection or disease. The acute inflammatory response is an essential mechanism that promotes healing and a key aspect is the ensuing pain, which warns the subject to protect the site of injury. Thus, it is common to see a zone of primary sensitization as well as consequential central sensitization that generally, is maintained by a peripheral drive from the zone of tissue injury. Inflammation associated with chronic pain states, such as rheumatoid and osteoarthritis, cancer and migraine etc. is deleterious to health and often debilitating for the patient. Thus there is a large unmet clinical need. The mechanisms underlying both acute and chronic inflammatory pain are extensive and complex, involving a diversity of cell types, receptors and proteins. Among these the contribution of voltage gated sodium and calcium channels on peripheral nociceptors is critical for nociceptive transmission beyond the peripheral transducers and changes in their distribution, accumulation, clustering and functional activities have been linked to both inflammatory and neuropathic pain. The latter has been the main area for trials and use of drugs that modulate ion channels such as carbamazepine and gabapentin, but given the large peripheral drive that follows tissue damage, there is a clear rationale for blocking voltage gated sodium and calcium channels in these pain states. It has been hypothesized that pain of inflammatory origin may evolve into a condition that resembles neuropathic pain, but mixed pains such as low back pain and cancer pain often include elements of both pain states. This review considers the therapeutic potential for sodium and calcium channel blockers for the treatment of chronic inflammatory pain states.

Contents

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1. Introduction

Inflammatory pain is largely treated with non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, opioids and steroids. These agents may be used in isolation or in combination depending on the nature and chronicity of the condition. The acute inflammatory response is controlled relatively efficaciously with these drugs, however inflammatory pain associated with chronic disease, such as rheumatoid and osteoarthritis, cancer and migraine etc. is deleterious to health and often debilitating for the patient. With regards to chronic inflammatory pain, and indeed neuropathic pain, these drugs have limited use and so a significant unmet clinical need for the treatment of chronic inflammatory pain remains [20,38,123].

Inflammatory pain results from the sensitization and activation of peripheral nociceptors by inflammatory mediators such as bradykinin, prostaglandins, nerve growth factor (NGF) and serotonin (5-HT); these accumulate in damaged tissue so that it becomes inflamed, hot, red and swollen, resulting in spontaneous pain and tenderness of the affected area. The actions of inflammatory mediators upon primary sensory afferents causes these neurons to have a lowered threshold for activation, increased responsiveness to a given stimuli and spontaneous discharge. Inflammation also recruits "silent" nociceptors, a class of nociceptors that are not normally excitable but become activated under inflammatory conditions [81,83]. This increased excitability of sensory afferents contributes to pain and hypersensitivity, featuring hyperalgesia (hypersensitivity to a painful input), allodynia (a painful response to low level innocuous stimuli) and spontaneous (ongoing) pain. These disordered sensory responses are also dependent on CNS mechanisms such as central sensitization within the spinal cord and plasticity within supra-spinal areas comprising the pain matrix [30,71,119], however the arrival of these peripheral messages within central synapses is contingent on ion channel activation in peripheral sensory afferents.

The mechanisms underlying inflammation-induced increase in afferent fiber excitability reflects, at least in part, changes in the density, distribution and/or expression of a variety of ion channels, including voltage gated sodium and calcium channels. These channels are the targets of many currently licensed drugs used for the treatment of chronic pain and, in contrast to inflammatory pain, are first line medications for the treatment of neuropathic pain. These drugs include gabapentinoids, carbamazepine, lamotrigine and topical lidocaine (for comprehensive list see [11,46]).

The therapeutic utility of sodium and calcium channel blockers, however, are not traditionally considered to treat pain of inflammatory origin, but given the large peripheral drive that follows tissue damage alongside abundant pre-clinical evidence implicating a role for voltage gated sodium and calcium channels in models of chronic inflammation and the indications of a neuropathic component to disease classically associated with inflammation, there may well be a rationale for their use. Indeed, lidocaine infusion, at plasma concentrations comparable to a lidocaine patch, reduced C-fiber spontaneous discharge and mechanical hyperalgeisa in a rat model of chronic inflammatory pain [127] and there is evidence for analgesic efficacy of lidocaine to treat low back pain and OA in patients [7,38,50–52], although this may relate to lidocaine's indirect anti-inflammatory properties as well as direct sodium channel modulation [65,133].

This review, therefore, will briefly summarize the role of voltage gated sodium and calcium channels, and the analgesic potential of blockers, in chronic inflammatory pain with additional reference to neuropathic pain, as these pain states despite very different peripheral originating drives may share common mechanisms, mostly central, which often coexist in patients with chronic inflammatory disease [128]. Furthermore mixed pains such as cancer pain and low back pain can share the full range of inflammatory and neuropathic mechanisms.

2. Chronic disease, inflammatory and neuropathic pain

The acute inflammatory response is a natural response of the body that occurs immediately following tissue damage, serving as an essential mechanism to promote healing and damage limitation of the injured area. Thus, it is common to see a zone of primary sensitization as well as consequential central sensitization that generally, is maintained by a peripheral drive from the zone of tissue injury. Inflammation associated with chronic pain states, however, does not heal and is deleterious to health. It has been hypothesized that pain of inflammatory origin may evolve into a condition that resembles neuropathic pain [128], since the persistence and severity of the disease state as it progresses could result in neuronal damage alongside tissue damage. Thus chronic inflammatory pain states, which often arise as a consequence of diseases like arthritis, cancer and possibly even migraine, or, in rare cases, as a consequence of genetic mutations [125], are indicative of inflammation alongside potential for nerve injury-like pains.

Arthritis - Osteorthritis (OA) and rheumatoid arthritis are degenerative diseases, which principally damage synovial joints. Inflammation (episodic and chronic) and swelling of joints are key symptoms of the disease as is significant pain. Both types can result in destruction of soft tissue and bone, hence potential for neural damage and, consequently, neuropathic pain exists. In line with this hypothesis, in the MIA model of osteoarthritis there is a dose-dependent increase in ATF-3 and a reduction in the intra-epidermal nerve density suggestive of neuropathy [66,117], and OA patients have used similar descriptors for their pain as neuropathy patients where a pain DETECT questionnaire identified subgroups of OA patients whose pain scores aligned with neuropathic-like pain [60,64,88]. Obviously, use of common descriptors may reflect common verbal consequences of a pain state rather than neuropathy per se.

Cancer - Pain is a major symptom for cancer patients, for instance tumors that metastasize to the bone are the most common cause of cancer pain, which includes background pain and severe pain on moving or weight-bearing [82]. Models of cancer in bone pain developed in rodents have shown that local destruction of the bone, peripheral nerves, and dorsal horn pathophysiology is indicative of a unique pain state, but neuropathy and inflammation are key components [56].

Erythromelalgia (EM) is a rare and frequently devastating neurovascular peripheral pain disorder in which blood vessels (usually hands or feet) are episodically blocked then become engorged with blood and inflamed, the patient experiences severe burning pain and skin redness. EM is subclassified into primary and secondary EM. Primary EM is a rare inherited condition caused by genetic mutations in the SCN9A gene that encodes the $Na_V1.7$ sodium channel α-subunit, and affects a very small proportion of EM patients [132]. The cause of secondary EM is often unknown but many patients have peripheral neuropathies [31,102]. The incidence of EM is low, with estimates ranging from 0.3 to 1.3 per 100,000 people per year [95], however, the associated pain and burning sensations can be extremely severe and is associated with diminished quality of life and considerable disability.

Migraine is a complex disorder of the brain where pain is a major symptom. Originally considered to be a vascular disorder, the definition is turning toward a neurogenic disorder caused by inflammatory mediators sensitizing dural afferents and affecting cranial blood vessels and possible central drives to the peripheral sequelae. Interestingly, symptoms associated with neuropathic

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pain such as allodynia are often reported during most well established migraine attacks [15,53].

Interestingly rare forms of congenital migraine, familial hemiplegic migraine (FHM), have been linked to mutations in the genes CACNL1A4 (FHM - type1) which encodes the α1 subunit of the neuronal voltage gated calcium channel subtype $Ca_V2.1$ [89], and SCN1A (FHM - type 3) which encodes the voltage gated sodium channel subtype $Na_V1.1$ [36].

Therapeutic management of these chronic diseases places a huge healthcare burden on society and with an increasingly elderly and obese population, these costs are set to rise with time. For many patients pain is the major symptom and often the first reason for clinical presentation and complaint, and since disease modification therapies remain either unavailable or suboptimal for many, analgesics remain as the first line of treatment of pain and inflammation [20,123].

3. Voltage gated sodium channels

The therapeutic advantage of targeting voltage gated sodium (Na_V) channels to treat pain is well known with abundant evidence demonstrating a critical role for these channels in pain transmission [33,39]. Na_V channels are essential for the initiation and propagation of action potentials and therefore neuronal conduction. Importantly, following transduction of tissue damaging and chemical stimuli, transmission will depend on sodium channels, thus pointing to these as important targets in pains from tissue damage. The direct modulation of transducers runs the risk of redundancy since there are multiple chemical mediators whereas altering transmission allows many peripheral sensors to be nullified.

A key consideration for the therapeutic use of Na_V blockers is a clear separation between cardiovascular and sensory neuronal effects without numbness. The identification of nine sodium channel subtypes is facilitating this possibility. Accordingly, $Na_V1.1$ and 1.6–1.9 are expressed in high levels in dorsal root ganglia (DRG) and hence most relevant in primary afferent transmission, and of these, the $Na_V1.7$-1.9 channels, are of particular interest, since they are preferentially expressed in peripheral neurons and have been linked to chronic inflammatory pain conditions (for review see [6,33,39]). These isoforms are also classified according to their sensitivity to tetrodotoxin (TTX). $Na_V1.1$, 1.6 and 1.7 are TTX sensitive (TTX-s) and $Na_V1.8$ and 1.9 TTX resistant (TTX-r). DRG neurones express multiple isoform combinations, and therefore underlie the diversity of TTX-s and TTX-r sodium currents seen in different neuronal subgroups [16].

The $Na_V1.7$ channel is expressed in sensory and sympathetic neurones and olfactory epithelial cells and is the main driver of the TTX-s current seen in small fibers, likely nociceptors [16,17,29]. Its gating kinetics allow for amplification of subthreshold depolarisations which then enables activation of $Na_V1.8$ channels and the firing of action potentials [25,98], thus $Na_V1.7$ acts as a threshold channel and increased receptor activity due to tissue or nerve injury would promote hyperexcitability of neurons to sub-threshold stimuli.

Several lines of evidence have firmly placed this channel in pain pathways, with a major contribution to inflammatory pain [35,84,85]. For instance, comparison of sodium channel expression within peripheral nerves supplying dental pulp in normal and inflamed human teeth revealed increased axonal expression and enhanced activity of $Na_V1.7$ at intact and remodeling/demyelinating nodes within the inflamed group. These changes were proposed to contribute to the constant, increased evoked and spontaneous pain that characterize toothache [76]. The most compelling evidence linking this channel in pain signaling, and specifically inflammation, comes from human genetic studies, where a gain of function mutation in the encoding gene, SCN9A, underlies the human pain state, primary erythromelalgia (see refs [35]). A different mutation in the SCN9A gene has been associated with a greater pain score in OA patients and those with sciatic pain due to a lumbar disk herniation and here in both groups, inflammation is an important component of their pain [96]. Yet another set of gain of function mutations in the SCN9A gene underlies paroxysmal extreme pain disorder, here patients experience episodes of severe burning pain of mandibular, rectal and ocular areas accompanied by skin redness and flushing [45]. Here there is a gain of function without nerve damage, which again, is reminiscent of patients with tissue damage. Interestingly, the converse situation can occur; a proportion of patients with small fiber neuropathy, with no apparent external cause, were linked with gain of function mutations of $Na_V1.7$ sodium channels. Here it is thought that the hyperexcitable nature of the DRGs, due to the increased $Na_V1.7$ channel activity, causes peripheral nerve degeneration [41], a similar possibility may exist for mutations of the SCN10A (encoding gene for $Na_V1.8$ α-subunit) and neuropathy [42].

A key issue is the ability of a drug to attenuate pain related sodium channel activity. Obviously drugs that are selective for a specific sodium channel subtype would be an attractive approach since there is greater potential for a low side effect profile and tolerability. Alternatively non-selective drugs, in terms of their sodium channel profile, could exert "selective" actions on those channels active in pain conditions by merit of use dependency. For example, drugs might target one or other conformational states of a channel, such as closed, open or inactivated. The kinetics and biophysical properties of an ion channel can depend upon the subtype and physiological conditions of activation. An advantage of targeting the functional state of the channel could be the ability to modulate more than one subtype but only when those channels are in a functional state that is induced by the pain condition and e.g. stabilize that channel in the inactive state. A disadvantage of this approach might be identifying the relationship between functional state, a given pain condition and drug action, which is likely to be trial and error.

The ability of non-specific sodium channel blockers, such as carbamazepine, lidocaine and mexilitine, to work in some but not other gain of function mutations suggests that they may exert their effects on a particular functional state [26,91,108,131] induced by a given mutation. In line with this hypothesis a recent study has suggested that alternative splicing of $Na_V1.1$ may relate to modifications in channel inactivation and the consequent efficacy of anti-epileptic drugs that stabilize sodium channel inactivation [47]. Thus these studies suggest a much broader role for mutations of peripheral $Na_V1.7$ and 1.8 sodium channels both in terms of neurological disease and as "druggable" targets. Teasing out their clinical utility will be challenging but could well pave the way toward individual pain therapy.

Alongside clinical data, preclinical studies uphold a role for $Na_V1.7$ and inflammatory pain. The fact that a loss of inflammatory pain phenotypes was obvious in animals with 1.7 and 1.8 knockouts and in mice where $Na_V1.7$ was deleted in a subset of $Na_V1.8$ expressing neurons further emphasizes the clear role of certain sodium channels in tissue damage pains [85,86]. The inflammatory mediator, NGF, produces an increase in $Na_V1.7$ expression, as does CFA and carrageen induced inflammation, an effect blocked by NSAIDs [18,57,58,111], and pain behaviors were blocked by peripherally acting selective $Na_V1.7$ blockers and via herpes vector knock down of $Na_V1.7$ in a CFA and formalin models of inflammatory pain in rodents [19,80,134]. Thus these studies support targeting $Na_V1.7$ channels for the treatment of chronic inflammatory pain. A recent pharmacological study, whereby XEN402, a reported antagonist of $Na_V1.7$ channels, significantly reduced pain scores in a small patient

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group with inherited erythromelalgia [55] apparently supports this hypothesis. However, without knowledge of the selectivity of this drug or the mechanism of Na_V blockade the potential of this data remains to be verified.

The $Na_V1.8$ is a tetrodotoxin resistant (TTX-r) voltage gated sodium channel, which contributes almost exclusively to the inward sodium current underlying the fast upstroke of action potentials in small diameter nociceptor-like neurons within DRG [97]. There is a large body of evidence linking $Na_V1.8$ channel activity with the initiation and maintenance of chronic inflammatory pain [6,39]. These include studies where inflammatory mediators such as NGF, prostaglandins, and serotonin etc. were shown to modulate TTX-r currents, sub-served by $Na_V1.8$ channels in DRG, to increase neuronal excitability to produce a leftward shift in the stimulus response curve [9,18,22,40,54]. Global and tissue selective knock-out of $Na_V1.8$ in mice with hind paw inflammation demonstrated altered channel expression in sciatic nerves, DRG, reduced pain behaviors and reduced or delayed inflammatory hyperalgesia [2,3,28,85]. Likewise, anti-sense knock down of $Na_V1.8$ following peripheral cutaneous inflammation [68,69] and visceral inflammation [63,70] reduced hyperalgesic pain behaviors and bladder nociceptive responses [136]. Hyperexcitability of DRG neurones, in a model of colitis, were also associated with an increase in $Na_V1.8$ current [13].

These findings led to the development of a small molecule selective blocker of $Na_V1.8$, A803467, which significantly attenuated hypersensitive behavior in a variety of animal models of inflammatory pain [67] including OA pain [105]. Improvements in the bioavailability of small molecule $Na_V1.8$ blockers holds promise for their analgesic potential in treating chronic inflammatory pain states [103,140]. Interestingly, neurogenic inflammation and subsequent sensitization of dural afferents is thought to trigger migraine pain. Evidence supports a role for ionic mechanisms involving modulation of TTX-r Na channels, likely $Na_V1.8$, in dural afferent sensitization. The channel is present on all dural afferents in which it appears to play the dominant role in spike initiation, thus a selective $Na_V1.8$ blocker could be effective for treating migraine pain [124].

A key driver for the development of $Na_V1.8$ blockers was its reported restricted expression to small diameter unmyelinated nociceptive neurons, however recent immunohistochemical data suggests that $Na_V1.8$ is not exclusive to nociceptors, but is, in fact, expressed in relatively high levels (approx. 40%) of myelinated A-fibers and also present on C-low threshold mechanoreceptors (C-LTMs) [109]. This does not negate its potential as an analgesic target, indeed the finding that mechanical hypersensitivity requires C-LTMS [106], highlights further the potential therapeutic utility of blocking this channel, but certainly a more careful description of it's neurobiology is needed to aid drug development with a favorable side effect profile.

The $Na_V1.9$ channel has also been implicated for the transmission of inflammatory pain although its role is less well documented compared with that of $Na_V1.7$ and 1.8 [77,99]. A more recently identified sodium channel, the $Na_V1.9$ is expressed in small diameter nociceptive sensory neurons in dorsal root ganglia and trigeminal ganglia [34], and contributes to a G-protein pathway-regulated TTX-r persistent current which can be activated by potentials close to resting membrane potential [32]. This persistent current is thought to drive spontaneous discharge in nociceptive nerve fibers during inflammation [62,90,122] and may contribute to setting inflammatory pain thresholds and activation of silent nociceptors [9,10].

Behavioral studies with $Na_V1.9$ null mice have shown a link between $Na_V1.9$ activity and inflammatory pain behaviors, although discrepancies exist with regards to modality specificity. For instance, a reduction in inflammatory induced thermal hypersensitivity and spontaneous pain behavior was reported in $NA_V1.9$ null mice without affecting mechanical pain responses [5,93], whereas a more recent study demonstrated a contribution to mechanical pain hypersensitivity induced by both sub-acute and chronic inflammatory pain models [74] yet others observed only a moderate and relatively short acting reduction in mechanical thresholds in $Na_V1.9$ null mice post inflammation [73]. In addition, $Na_V1.9$ may play a role in the maintenance stage of inflammatory pain since channel up-regulation was seen during the later time points in a model of chronic joint inflammation compared with no change during the initiation phase [111], but see [73]. Despite these discrepancies a rationale for modulating $Na_V1.9$ channels in chronic pain states remains attractive and development of selective blockers are needed to continue to probe its analgesic potential in chronic inflammatory pain settings.

4. Voltage gated calcium channels

Voltage gated calcium channels (VGCCs) are expressed on virtually all excitable cells and whose activity is critical for neurotransmitter release, the regulation of neuronal excitability and intracellular changes including gene induction [23,126]. Ten subtypes have been cloned and sensory neurons express a number of classes of VGCCs. These channels are classified as L (Ca_V 1.1–1.3), N (Ca_V 2.2), P/Q(Ca_V 2.1), and R-type (Ca_V 2.3), which are high voltage activated and T-type (Ca_V 3.1–3.3), which underlie low voltage activated currents [137]. Studies have implicated an increase in voltage-gated Ca^{2+} currents, and their potential redistribution to central or peripheral terminals, contributing to inflammation-induced increases in afferent input [14,75,87,115] although an inflammation induced down regulation of N-type channels has also been reported, but only on a specific subset of sensory neurones [100].

The roles of N-, P/Q- and T-type, as well as the auxiliary $\alpha 2\delta$ subunits, have been most extensively studied with regards to chronic pain [104,114,116,129,139]. The N-type (Ca_V 2.2) is of particular interest since it is concentrated in laminae I and II, of the superficial dorsal horn, where nociceptive primary afferents synapse, an enhanced nociceptive role is seen after inflammation and neuropathy [78,79,129] and genetic deletion attenuates inflammatory pain behaviors [101]. Further, N-type channel blockers reduced hyperexcitability of dorsal horn neurons, as well as the behavioral hyperalgesia in animal models of inflammatory and neuropathic pain [79,107,121,130], and splice variants of the N-type channel, namely splice variant exon 37a, generates a novel form of the N-type channel that is highly enriched in nociceptive neurons and is required for the development of thermal and mechanical hyperalgesia during inflammatory and neuropathic pain [4].

The N-type ($Ca_V2.2$) blocker ziconitide (Prialt^{TM}) is licensed for the treatment of intractable pain, but is of limited use due to its narrow therapeutic window and it must be delivered intrathecally. However, the discovery of new small-molecule inhibitors of Ca_V 2.2, such as the orally available state-dependent blocker N-triazole oxindole (TROX-1), is improving therapeutic pharmacology. TROX-1 reversed inflammatory-induced hyperalgesia with maximal effects equivalent to NSAIDs, and reversed nerve injury-induced allodynia to the same extent as pregabalin and duloxetine. In contrast, no significant reversal of hyperalgesia was observed in $Ca_V2.2$ gene-deleted mice. Mild impairment of motor and cardiovascular functions was only observed at concentrations much greater than that required for analgesia [1].

A different approach from targeting the channel pore is exemplified by interest in the role of collapsin response mediator protein, CRMP-2. This is a modulator of $Ca_V2.2$ and over-expression of CRMP-2 was shown to increase calcium currents and membrane

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expression of $Ca_V2.2$, and conversely knockdown of CRMP-2 produced the opposite effect. Uncoupling the interaction between CRMP-2 and $Ca_V2.2$ reduced calcium current, neurotransmitter release and inflammatory and neuropathic hypersensitivity [21]. Thus these and other studies support further exploitation of N-type blockers/modulators of channel activity, for the treatment of inflammatory pain as well as neuropathic pain [1,21,120,138]. Interestingly it has been recently proposed that the selective 5-HT_1 receptor agonist sumatriptan, effective for the treatment of migraine pain, exerts its effects via blockade of N-type calcium channels [8].

The T-type calcium channels ($Ca_V3.1$–3.3) are activated at low thresholds, close to resting membrane potential, and thus play an important role in modulating neuronal excitability and hence nociceptive signaling at all levels from the periphery to the brain; an increase in T-type currents has been associated with decreased nociceptive threshold [118,139]. Compounds with modest T-type inhibition such as ethosuximide and mibefridl and newer more potent and selective T-type blockers such as KST5468 and T-type channel antagonists (TTA), TTA-A2, and TTA-P2 have antinociceptive efficacy in inflammatory models, reducing paw edema and immune cell number [14,24,48,72,92].

The $Ca_V3.2$ subtype is a particularly attractive analgesic target, since it is expressed primarily in DRGs, localized to nerve endings, and is thought to play a selective role in pro-nociceptive transmission, with significant evidence linking this channel to the pathophysiology of both inflammatory and neuropathic pain [118,139], but a lack of selective pharmacological blockers has impeded full understanding of the neurobiological properties and therapeutic utility of targeting this subtype. However a recent report detailing the analgesic efficacy of a small organic state-dependent T-type channel antagonist, TTA-A2, in thermal nociceptive test and a model of IBS pain, which despite being a pan Ca_V3 blocker, efficiently inhibits recombinant human and native DRG $Ca_V3.2$ currents, and has greater potency for $Ca_V3.2$ compared to $Ca_V3.1$. Thus there is promise for the future development of true selective blockers and potentially novel analgesics with better side effect profiles [48].

Blockade of VGCC activity is considered the primary mechanism of action of analgesics such as gabapentin and pregabalin – first-line treatments for neuropathic pain [46]. These drugs uniquely reverse conditions of neural sensitization such as after nerve injury without affecting normal physiological pain [37]. Their exact analgesic mechanism, remains unclear, but are known to bind to the $\alpha2\delta1$ accessory subunit of VGCCs, an upregulation of which occurs in the DRG and spinal cord after neuropathy. It has been suggested that gabapentinoids exert their analgesic effect by blocking trafficking of $\alpha2\delta1$ to synaptic terminals in the spinal cord of neuropathic rats [12,61].

There are some reports of changes in the expression of the $\alpha2\delta$ subunit in inflammatory settings also. For instance, persistent inflammation induced by CFA resulted in an increase in both $\alpha2\delta1$ and $Ca_V2.2$ protein detected in the central nerves arising from L4 and L5 ganglia ipsilateral to the site of inflammation [75]. A modest but significant increase (but far less than that seen after neuropathy) in $\alpha2\delta1$ mRNA levels was seen in ipsilateral L3 & 4 DRG in a rat model of knee osteoarthritic pain, this was accompanied by a clear inhibition of dorsal horn neuronal responses by pregabalin [94], and an increase in ATF3, a marker for nerve injury, in ipsilateral DRG innervating the arthritic knee [66,117]. However, in the latter study, using a lower dose of MIA, there was no sign of nerve damage and pregabalin was ineffective. Similarly, in a rat model of rheumatoid arthritis, mechanical allodynia that developed in line with joint inflammation and swelling, remained after resolution of inflammation and was blocked by gabapentin [27]. Further an increase in ATF3 was also only seen at the late stage of the model when inflammation had resolved, however the authors did not assess $\alpha2\delta1$ levels in this study. These studies modeling chronic inflammation suggest the possibility of transition toward certain mechanisms seen in a neuropathic state, suggesting potential therapeutic utility of gabapentinoids, and other drugs with analgesic efficacy for treating neuropathic pain, in the treatment of chronic inflammatory pain states also. Furthermore, it should be noted that studies exist demonstrating antinociceptive efficacy of gabapentinoids on behavioral and neuronal pain responses in formalin and carrageenan models of acute inflammatory pain [110,116,135] where any neuropathic component is unlikely and therefore suggest a mechanism independent of $\alpha2\delta1$ up-regulation. Another mechanism considered permissive for the state dependent action of $\alpha2\delta$-ligands is the active participation of descending serotonergic pathways that facilitate spinal neuronal activity via activation of excitatory spinal 5-HT3 receptors [112]. In line with this hypothesis, spinal 5-HT3 receptor activity is enhanced in formalin and MIA models of pain where $\alpha2\delta$-ligands are antinociceptive [59,94,113,116]. Given that inflammation is a key component in these animal models of pain, and that calcium channel blockers such as azelnidipine and lercanidipine reduce inflammation in patients [43,44,49] and so might indirectly influence pain, again highlights the potential for the clinical utility of VGCC blockers and treatment of chronic inflammatory pain.

5. Conclusion

Voltage gated sodium and calcium channels on peripheral nociceptors clearly have major roles in the mediating the pain associated with acute and chronic inflammation. Further, chronic disease conditions such as cancer have pain that is initiated and maintained via both inflammatory and neuropathic mechanisms, and chronic disease classically considered to be of inflammatory origin may well progress in severity to encompass a neuropathic component. Thus voltage gated sodium and calcium channel modulating drugs, licensed for the treatment of neuropathic pain, could prove beneficial in the treatment of chronic inflammatory pain. Further, development of small molecule, orally available isoform selective blockers, targeting $Na_V1.7$, $Na_V1.8$, N-type (Ca_V 2.2) and T-type ($Ca_V3.2$) in particular, holds promise for future chronic pain management and a strategy to evaluate the therapeutic utility of these novel compounds for the treatment of chronic pain of inflammatory origin may yield promising results.

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