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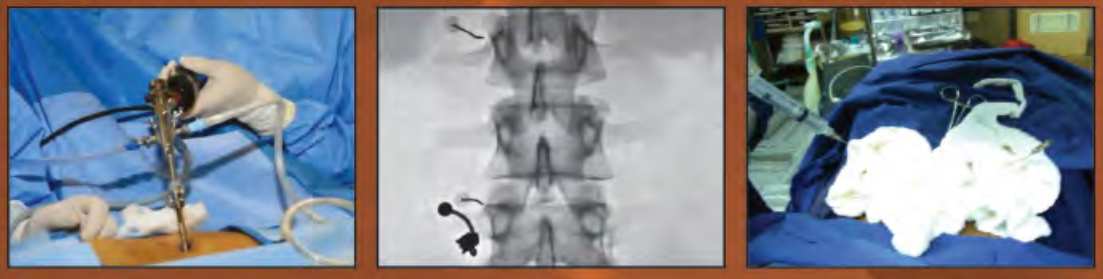

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Contents

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Neurobiology of Persistent Pain: Recent Advances

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ABSTRACT

Plasticity is inherent within the nervous system. Such plasticity underpins the development of persistent pain following a primary insult. The mechanism by which this occurs is complex and has components within the peripheral and central nervous system. In general, nociceptive neuronal hypersensitivity develops as a result of positive feedback loops, descending facilitation, and loss of inhibitory modulation at the spinal and supraspinal level. This article will focus on various neurobiological elements currently felt to be key to this process. Understanding this process as a pathological phenomenon as opposed to passive transmission has identified numerous targets for therapeutic intervention (pharmacological, psychological, and surgical) and allowed an advance towards rational treatment within the field of pain medicine.

INTRODUCTION

Persistent or chronic pain can be inflammatory or neuropathic and is the result of aberrant functioning of the peripheral or central nervous systems (CNS) that has been pathologically modified. It is not directly related to a noxious stimulus and persists beyond the tissue damage that initiated the pain. The characteristics of the pain, hyperalgesia, and allodynia reflect peripheral and central sensitization of the nociceptive pathways. The fundamental science underpinning persistent pain perception is a continuously evolving field with a bewildering complexity. The diverse range of chemical mediators, cell types, receptors, ion channels, secondary

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messenger pathways, and novel neural connectivity investigated and implicated, makes a clear sequential explanation that links stimulus to perception, a target far beyond the capacity of a single chapter. Instead, using a simplistic pain pathway as a clothes line, we will peg an overview of current concepts along its length and hope the reader and the line are not weighed down by the meandering and sometime overlapping explanations of this pathological phenomenon.

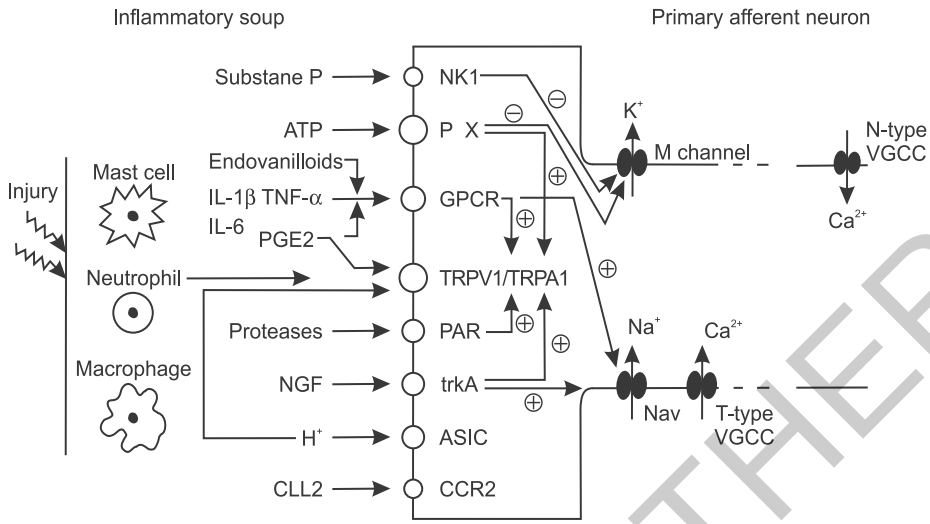
FROM THE NOCICEPTOR TO THE SPINAL CORD

In the majority of cases, persistent pain begins with a peripheral insult producing an inflammatory response with or without nerve injury. There is then increased excitability of primary nociceptive afferents towards threshold for action potential generation, and in some instance, to the point where action potentials develop spontaneously. The resulting increased action potential frequency in combination with facilitation of excitation-secretion coupling in the dorsal horn increases release of excitatory neurotransmitters and so activation of the central components of the nociceptive pathway. Critical to this peripheral sensitization is an inflammatory process that amplifies and prolongs the impact of the initial insult: the inflammatory soup—the receptors that mediate the influence of this soup become hypersensitive to noxious and non-noxious stimuli and allow drift of the membrane potential toward threshold; transient receptor potential (TRP) ion channels and acid sensing ion channels (ASICs); and the voltage-gated ion channels—the activity of which influences the resting membrane potential, action potential initiation and propagation, and neurotransmitter release—voltage-gated Na^+, K^+, and Ca^{2+} channels (Figure 1).

The Inflammatory Soup

Apart from activating the nociceptive neuron and producing an action potential, noxious stimuli can also cause tissue damage and inflammation. The activated and in some cases damaged neurons, along with resident and recruited inflammatory cells (including mast cells, monocytes and macropahges, neutrophils, platelets, and endothelial cells) and the released inflammatory mediators [including arachidonic acid derivatives, cytokines, chemokines, peptides (substance P, bradykinin, calcitonin gene-related peptide), proteases, protons, and purinergic acids] form what is collectively described as an inflammatory soup.

The presence of inflammation is significant in both inflammatory and neuropathic pain, meaning that pathophysiological distinction between the two syndromes is blurring. Immune cells and the released mediators appear to have pivotal roles in the development of peripheral sensitization.[1] Apart from the classical immune cells, mast cells, neutrophils, macrophages, and T-cells in nerve injury Schwann cells appear to be fulfilling an immunological role releasing



ATP, adenosine triphosphate; NK1, neurokinin 1; P2X, purinergic receptor; trkA, tropomyosin receptor kinase A; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; PGE2, prostaglandin E2; NGF, nerve growth factor; CLL2, chemokine ligand 2; GPCR, G protein-coupled receptor; TRPV1, transient receptor potential vanilloid 1; TRPA1, transient receptor potential ankyrin 1; PAR, protease activated receptor; ASIC, acid sensing ion channel; CCR2, chemokine receptor 2; Nav, voltage-gated sodium; VGCC, voltage-gated calcium channel.

Figure 1: Factors influencing primary afferent neuron sensitivity and excitability. Injury activates inflammatory cells and neurons causing the release of inflammatory mediators (IL-1β, IL-6, TNF-α, proteases, PAR, NGF, endovanilloids, H^+, PGE2, and CLL2) and neuropeptides (ATP and substance P). These factors bind to a number of receptors (NK1, P2X, GPCR G, PAR, trkA, ASIC, and CCR2) in the cell membrane of the afferent neuron. This leads to sensitization of the TRPV1 and TRPA1, and increased neuronal excitation by inhibiting M channels and stimulating Nav.

cytokine and phagocytosing debris. Stabilization of mast cells and reduction in infiltration by neutrophils, macrophages, and T cells have all been shown to reduce the development of hyperalgesia and allodynia.[2-5] The role of Schwann cells is slightly more complex. Reduction in tumor necrosis factor-α (TNF-α) expression by Schwann cells reduces neuropathic pain[6] and disruption of ErbB expression; a tyrosine kinase important in Schwann cell–neuron interaction caused loss of thermal hypersensitivity in nonmyelianted cells.[7] However, disruption of ErbB expression in myelinated cells produced mechanical allodynia.[8]

With respect to inflammatory mediators, significant candidates include interleukin-1β (IL-1β), TNF-α, IL-6, chemokine ligand 2 (CLL2), prostaglandin E2 (PGE2), adenosine triphosphate (ATP), and nerve growth factor (NGF). IL-1β and TNF-α both induce neuropathic pain on direct injection,[9,10] and impairment of their signaling attenuates neuropathic phenomenon.[11-13] IL-1β has a number of speculated sites of action: inducing the release of more inflammatory mediators generating positive feedback[14] as well as causing direct

neuronal excitation[15] and stimulating the release of the neuropeptides substance P and calcitonin gene related peptide (CGRP),[16,17] which activate voltage-gated sodium (Nav) channels. TNF-α may increase excitation through p38 mitogen kinase mediated phosphorylation of Nav channels (see below). The role of IL-6 is a little less clear since knockout mice exhibit reduced hyperalgesia and allodynia,[18] but peripheral application has an antinociceptive effect.[19]

Two chemokines having a significant role in persistent pain are CLL2 and fractalkine. CLL2 is expressed by macrophages, Schwann cells, and neurons.[1] Fractalkine is secreted primarily by neurons and mediates a significant interaction between neurons and microglia in the dorsal horn (see below). CCL2 is upregulated following nerve injury.[20] Null mutants without the required receptor [chemokine receptor 2 (CCR2)] have significantly attenuated pain behavior[21] and intraneural administration produces transient mechanical allodynia and thermal hyperalgesia.[22] There is evidence that CLL2 is able to excite dorsal root ganglion (DRG) neurons directly[23] and reduces inhibitory γ-aminobutyric acid (GABA)-ergic currents.[24] PGE2 activates Nav channels and has a role in central sensitization (see below).

ATP is released from damaged cells and binds to distinct purinergic receptors found on nociceptive neurons and immune cells. Blocking these receptors blunts neuronal excitability and thermal and mechanical hypersensitivity. It appears that ATP acts by activating Nav channels and stimulating the release of inflammatory cytokines.[25]

NGF has a significant and multifaceted role. NGF sensitizes nociceptive neurons as emphasized by the mutation of its tropomyosin receptor kinase A (trkA) resulting in insensitivity to pain[26] and systemic administration triggering thermal and mechanical hyperalgesia.[27] NGF sensitizes TRP vanilloid 1 (TRPV1) receptors via phospholipase C (PLC) activation and stimulation of an increase in TRPV1 expression (see below). It also increases the expression of Nav channels[28] and stimulates proliferation of immune cells (mast cell, lymphocytes, and neutrophil).[1] An NGF antagonist, tanezumab, a monoclonal antibody is currently being trialed for osteoarthritis and other chronic pain conditions (e.g., low back pain, diabetic peripheral neuropathy, and interstitial cystitis). These trials had been temporarily suspended due accelerated osteoarthritis and osteonecrosis. However, subsequent case review indicated that these phenomenona were due to pretreatment disease rates, increased utilization of the effected limb due to improved analgesia, and the inhibition of bone repair by coadministered nonsteroidal anti-inflammatories.[29]

The Receptors

The primary afferents have a role as a nociceptor converting the physical experience of a noxious stimulus into an action potential. This is achieved via a variety of transducing receptors broadly divided into those detecting temperature

changes, mechanical stimuli, and chemicals. The majority of these receptors are members of the TRP ion channel family. Twenty unique ion channels have been identified.[30] They are made of subunits with 6 membrane spanning domains and the amino acids linking the 5th and 6th domains forming an ion channel. This ion channel is relatively nonselective being permeable to monovalent cations and calcium, and allows these to enter along their concentration gradient when the cell is hyperpolarized. This increases neuronal excitability by 2 mechanisms. It shift the membrane potential towards 0 mV and so towards the threshold for action potential initiation, and also via calcium dependent mechanisms, leading to transduction of ion channels to the membrane as well as increasing their activation and expression.

Activation and upregulation of 2 TRPs, TRPV1, and TRP ankyrin 1 (TRPA1) has been implicated in peripheral and central sensitization. Apart from responding to noxious stimuli, they are also activated by inflammatory mediators and protons. Clearly, supraphysiological activation is not a ubiquitous process, since only minorities of patients with nerve lesions, for example, develop neuropathic pain. This may relate to genetic susceptibility, and there is evidence to suggest that polymorphism in TRP genes is significant at least in determining pain characteristics, if not overall susceptibility.[31]

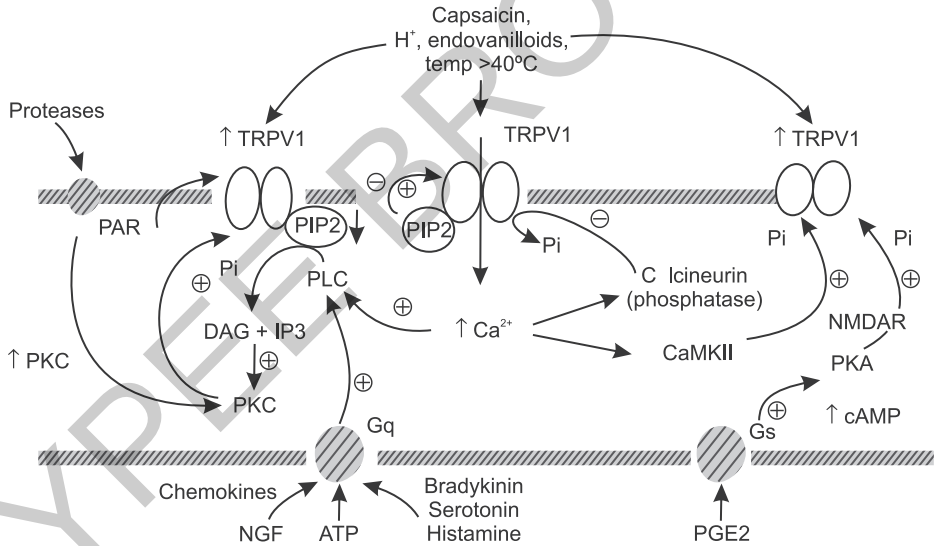
ASIC are another ligand-gated ion channel that may have a role in persistent pain. ASIC are cationic channels, largely sodium specific that are activated by the binding of protons allowing an influx of sodium ions and membrane depolarization.[32] They have been specifically linked to inflammatory pain,[33] but as discussed, the inflammation is also integral to neuropathic pain.

Transient Receptor Potential Channels

TRPV1 is found on the peripheral nerve terminal, in all sensory ganglia, in the dorsal horn and various regions of the brain [rostral ventral medulla (RVM), periaqueductal gray (PAG), amygdala, nucleus tractus solitarius, somatosensory cortex, anterior cingulated cortex (ACC), and insula]. It is classified as a thermoreceptor along with TRPV2-4, TRP melastin 8 (TRPM8), and TRP ankyrin 1 (TRPA1), and is activated by a heat (>40°C) causing opening of the cation channel. Numerous studies have indicated that TRPV1 plays a significant role in noxious heat detection and thermal hyperalgesia but knockout animals retain some sensitivity which is attributed to the other TRPV subtypes (TRPV2 around 52°C and TRPV3 and TRPV4, 25–35°C).[34] The mechanism of heat mediated opening remains unclear. There is a suggestion that conformational change is solely a thermodynamic phenomenon but transferring the C-terminal domain between channel types transfers heat threshold characteristics.[35] TRPV1 is also gated by protons (pH <5.2) and numerous chemical ligands. These

ligands include vanillioids (e.g., capsaicin—chilli) and other natural compounds (piperine—black pepper; zingerone—horseradish, and allicin—garlic and onions), and endovanilloid (anandamides) found in the inflammatory soup. The presence of hydrogen ions and endovanilloids in the inflammatory soup lowers the temperature threshold contributing to thermal hyperalgesia in inflammation.[36,37] Upregulation of TRPV1 has been demonstrated in inflammatory and neuropathic conditions and models, and there is attenuation of hyperalgesia in knockout animal suggesting a significant role in persistent pain.[38-41] The influence of inflammatory mediators is largely via modulation of mechanisms that control TRPV1 sensitivity to ligand binding and expression.

The sensitivity of TRPV1 is dependent on a number of factors, none of which have definitive control. Firstly, phosphorylation mediated by protein kinase C (PKC), protein kinase A (PKA), and Ca^{2+}/calmodulin (CaM)-dependent kinase/calneurin phosphatase balance. Secondly, phosphatidylinositol bisphosphonate (PIP2), CaM, and ATP binding, and thirdly, the protease activated receptors 1 and 4 (PAR 1 and 4) (Figure 2).



PAR, protease activated receptor; PKC, protein kinase C; PKA, protein kinase A; TRPV1, transient receptor potential vanilloid 1; DAG, diacylglycerol; IP3, inositol triphosphate; PLC, phospholipase C; PIP2, phosphatidylinositol bisphosphonate; phosphatidylinositol bisphosphonate; NGF, nerve growth factor; ATP, adenosine triphosphate; PGE2, prostaglandin E2; cAMP, cyclic adenosine monophosphate; NMDAR, N-methyl-D-aspartic acid receptor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II.

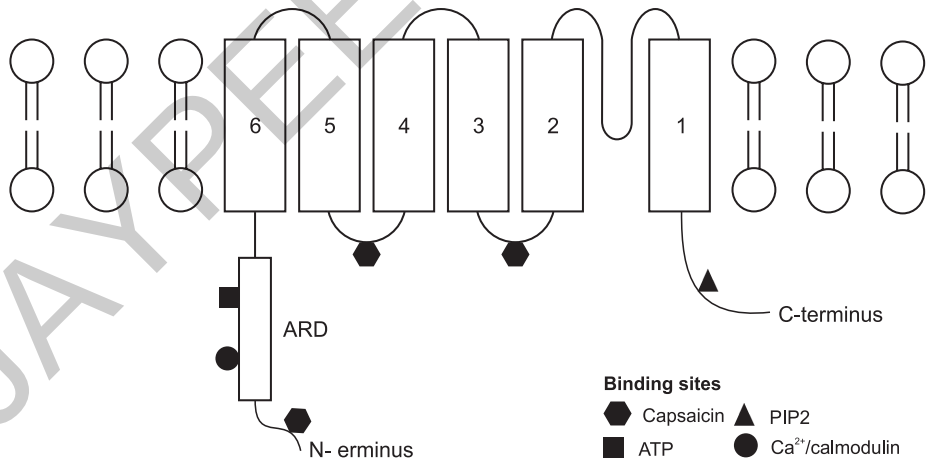
Figure 2: Modulation of TRPV1 activity. TRPV1 is activated by heat, H^+, exogenous (capsaicin), and endogenous (endovanilloids) factors. Sensitivity is controlled by phosphorylation by PKC, PKA, and CaMKII. PKC is activated by Ca^{2+}, PLC activated by Ca^{2+} and Gq-coupled receptor binding inflammatory mediators, and PAR. PKA is activated by a Gs-coupled receptor binding PGE2. CaMKII is activated by Ca^{2+}. TRPV1 is inhibited by dephosphorylation mediated by Ca^{2+} activated calcineurin and by hydrolysis of PIP2.

Proinflammatory mediator, such as NGF, ATP, bradykinin, serotonin, histamine, proteases, and chemokines cause phosphorylation of TRPV1, increasing the channels sensitivity.[42] These mediators activate PLC via a Gq linked receptor. PIP2 is hydrolyzed to diacylglycerol (DAG) and inositol triphosphate (IP3), and DAG activates PKC which then phosphorylates a serine residue on TRPV1.[43] In addition, PLC hydrolyses an inhibitory PIP2 constitutively associated with the receptor contributing to sensitization.[44]

However, PIP2 probably also has an excitatory role. Following high dose capsaicin, which desensitizes TRPV1 receptors, PIP2 synthesis is important for recovery.[45] Also, high dose capsaicin appears to produce TRPV1 desensitization by inducing Ca^{2+} influx via the receptor and activating PLC which depletes PIP2 levels.[42]

PIP2 binding occurs at the C-terminus of the receptor. Binding at the N-terminus are CaM and ATP in an area called the ankyrin repeat domain (ARD). Their binding in the ARD causes desensitization of the receptor. Cysteine residues in the N-terminus also appear to be the target for the naturally occurring compounds, including capsaicin (although this also binds to residues between the 2nd and 3rd and 4th and 5th domains)[46] (Figure 3).

PKA appears to sensitize TRPV1 by phosphorylating combinations of serine and threonine residues.[47] PKA is activated by a G protein-linked prostaglandin receptor that increases cyclic adenosine monophosphate (cAMP).[47] TRPV1 does not have a specific binding site for PKA, so for this to occur, PKA is brought into proximity with the TRPV1 receptor by protein kinase anchoring protein, which is coexpressed with the receptor and may bind directly to it.[48] The activation of



ARD, ankyrin repeat domain; PIP2, phosphatidylinositol bisphosphonate; ATP, adenosine triphosphate.

Figure 3: Structure of transient receptor potential ion channel vanilloid 1. Consists of 6 membrane spanning domains. The ion channel is located between domain 1 and 2.

PKA and so TRPV1 sensitization can be inhibited by the binding of opioids to μ-receptors.[49]

Calcium influx and increasing intracellular calcium may regulate further TRPV1 sensitization by calcium-dependent activation of PLC and 2 other opposing enzymes calcineurin and calmodulin dependent protein kinase. Calcineurin, a CaM-dependent phosphatase inactivates TRPV1 by dephosphorylation.[50] CaM-dependent protein kinase activates the channel by phosphorylation of sites targeted by PKC and PKA.[51] Apart from reducing the sensitivity of TRPV1 receptors, capsaicin also reduces nerve action potential transmission by reducing the density of all voltage-gated calcium channels. It appears that this is mediated by calcineurin-mediated dephosphorylation.[52]

PARs are G-protein-linked receptors activated by proteases (e.g., thrombin and trypsin) released as a result of inflammatory processes. PAR1 and PAR4 are located on a fraction of primary sensory neurons (15 and 8%, respectively). Activation leads to translocation of PKC to the cell membrane and sensitization of the TRPV1 channels. It also enhances the release of a proinflammatory neuropeptide CGRP. NGF increases the number of PAR1 and PAR4 expressing neurons.[53]

In addition to being associated with opening of TRPV1 channels in the membrane, sensitization in inflammatory and neuropathic pain is also the result of upregulation of gene translation and movement of assembled TRPV1 channels from intracellular storage to the cell membrane. These processes are stimulated by NGF and mediated by p38 mitogen-activated protein kinase (MAPK) and phophoinositide-3-kinase-src kinase.[54-56] In neuropathic pain, there appears to be downregulation of TRPV1 in the damaged neurons and upregulation in the undamaged ones.[39]

TRPV1 channels are also found on glial cells in lamina I and II and may contribute to their proliferation, which is known to be significant in central sensitization (see below). TRPV1 knockout mice show fewer cells in models of inflammatory and neuropathic pain.[57]

Within the CNS, TRPV1 has an inhibitory role.[58] Within the dorsal horn, TRPV1 receptors are found postsynaptically on lamina II cell bodies and excite inhibitory neurons enhancing GABA and glycine release. Also within the brain, TRPV1 channels are found in areas that mediate antinociception (locus coeruleus neurons, ACC, and PAG). Application of agonists and antagonists topically, systemically, and via intracerebroventricular injection, and microinjection into particular brain areas has demonstrated the significance of these channels in this role. Immunoreactivity has indicated that the TRPV1 channels are located on glutamatergic neurons that may receive input from GABAergic neurons. The antinociceptive effects of TRPV1 activation in these areas appear to be glutamate dependent.

TRPV1 receptors are currently a target for treatment in the form of capasacin. The rationale for using an agonist, as alluded to above, is that induced opening of TRPV1 channels leads to depletion of PIP2 precluding further pathological activation and decreases excitability via reduction in voltage-gated calcium channels. However, this induces unpleasant sensations in the first instance and so is not always well tolerated. An alternative is systemic antagonists, which have been shown to be effective in models of neuropathic and inflammatory pain.[59,60] A dose-limiting factor for many, however, has been hyperthermia as TRPV1 also appears to be critical for temperature control, although an antagonist without this problem has been identified.[61]

An alternative approach to desensitization and antagonism is hypersensitization. Persistent TRPV1 activation leads to a prolonged increase in intracellular calcium, which has a deleterious effect on the TRPV1 expressing cells. Therefore, targeting neurons, which are overexpressing TRPV1 leading to hyperalgesia and allodynia with a potent agonist would eliminate those neurons and the pain. Resiniferatoxin (RTX), an example of such an agonist has been shown to selectively ablate vanilloid sensitive neurons while leaving other adjacent neurons unaffected.[62] As stated previously, it is the undamaged neurons that exhibit TRPV1 upregulation, and so targeting these for destruction appears counterintuitive. However, RTX injected into the dorsal root and trigeminal ganglia has produced analgesia in inflammatory and neuropathic models without effect on touch, proprioception, mechanociception, or motor function.[62]

Polymorphism in TRPV1 may contribute to variation in persistent pain presentation. Analysis of TRPV1 gene variants in neuropathic patients has identified two key loci, 1911 lying within the ion channel and 1103 within the ARD.[31] 1911 A>G polymorphism was associated with altered heat pain threshold; AA and AG genotypes showing hyperalgesia. 1103 C>G polymorphism was associated with altered cold threshold, and CG genotype exhibited cold hypesthesia.

TRPM8 is a cold transducer. Like TRPV1, it is activated by temperature change (<25°C) but also by natural ligands, such as menthol. It is located on separate neurons to TRPV1.[63] Knockout mice demonstrate a significant but not complete deficit in cold response at the cellular, nerve fiber, and behavioral level. The residual sensitivity is accounted for by another TRP channel TRPA1 (<15°C).[64]

PKC appears to inactivate TRPM8.[65] This occurs directly by hydrolysis of PIP2 which maintains TRPM8 in an open state,[66] and indirectly by the activation of a calcineurin, which dephosphorylates TRPM8.[65]

Cold allodynia is a feature of neuropathic pain and it is logical that sensitization and increased expression of DRG, TRPM8, and TRPA1 would play a part in this. However, in neuropathic models that demonstrate allodynia in response to cold

and menthol, TRPM8 and TRPA1 expression decreases, and there is no increase in channel activity as measured by calcium influx.[67] This phenomenon, therefore, may develop at the spinal[67] or supraspinal level as suggested by recruitment of the dorsolateral prefrontal cortex (DLPFC) and midbrain noted on functional magnetic resonance imaging (fMRI).[68] TRPM8 actually appears to have an analgesic role, since cooling and low dose menthol, which reduce the thermal hyperalgesia and mechanical allodynia in neuropathic models, are ineffective in TRPM8 knockouts.[69]

Noxious cold sensation may also be influenced by potassium channels. A specific potassium channel blocker has been shown to increase the threshold for cold sensitive neurons and reduce the behavioral response to cold without influencing effect of heat and mechanical stimuli.[70]

TRPA1 is a TRP channel implicated in the transduction of cold (<15°C), mechanical, and chemical stimuli. It is coexpressed on peripheral nociceptive afferents with TRPV1.[63] A structurally diverse range of compounds are able to activate the channel, binding covalently to cysteine residues in the extended ARD at the N-terminus.[71] These include an allicin (garlic and onions), cinnamaldehyde (cinnamon oil), allyl isothiocyanate (mustard oil), and acrolein (wood and tobacco smoke, tear gas, and car exhaust).

Unlike TRPV1, which with exception of protons and endovanilloids, is only sensitized by inflammatory mediators, TRPA1 can be directly activated and indirectly sensitized by multiple endogenous inflammatory mediators.[72] Like TRPV1, sensitization is mediated by PLC and PIP2 hydrolysis[73] and upregulation in TRPA1 membrane expression occurs via a p38 MAPK pathway triggered by NGF.[74]

TRPA1 appears to have a significant role in persistent pain. Mutation in the gene coding TRPA1 has been recently identified in an autosomal dominant condition with episodes of debilitating upper body pain triggered by fasting and physical stress (familial episodic pain syndrome).[75] Knockdown and antagonist studies in models of inflammatory and neuropathic pain demonstrate that TRPA1 mediates mechanical hypersensitivity and cold hyperalgesia.[64,74,76,77] Peripheral and intrathecal infiltration of antagonists suggest that hyperalgesia is a result of peripheral expression and allodynia a central expression.[78] As with TRPV1, polymorphism may be relevant. Analysis of TRPA1 gene variants in neuropathic pain demonstrated that 710G>A was associated with paradoxical heat sensation.[31]

Activation of TRPA1 and TRPV1 by anesthesia could contribute to postoperative pain. Airway irritation associated with isoflurane and desflurane and pain on intravenous injection of propofol and etomidate have been attributed to TRPA1 activation.[79] Local anesthetic infiltration (lignocaine and bupivacaine) activates TRPV1 and to a lesser extent TRPA1.[80] While these effects are short lived, such activation may lead to peripheral and central sensitization.[79]

Acid-sensing Ion Channels

ASIC3 is a subtype located on nociceptive neurons in cardiac and skeletal muscle.[81] It is particularly sensitive to lactic acid[81] and mediates cardiac ischemic pain[82] and chronic hyperalgesia in injured skeletal muscle.[83] In cardiac muscle, 80% of ASIC3 muscle afferent neurons co-express CGRP, which is a vasodilatory peptide, suggesting capability for modulating blood flow in response to ischemia.[84]

There is, however, some conflicting evidence with respect to persistent pain. ASIC1, 2, and 3 knockout studies have demonstrated no or increased primary hyperalgesia rather than a decrease as might be expected.[85,86] There is evidence, however, that ASIC3 may have a role in central and peripheral sensitization. Inflammation initiated in the muscle of one limb increases ASIC3 expression in the DRG bilaterally and this expression is required for secondary hyperalgesia in the ipsilateral and contralateral limb.[33] ASIC3 micro-RNA (miRNA) (inhibits native mRNA translation) introduced into a muscle by a viral vector prior to inducing inflammation prevents primary and secondary hyperalgesia and reduced ASIC3 mRNA expression in the DRG.[87] ASIC1 also mediates primary hyperalgesia in the inflamed muscle.[33]

The role of ASIC2 may be modulatory. Like ASIC3, its expression is increased bilaterally in the DRG during inflammation. However, inhibition leads to hyperalgesia. It may, therefore, have a central inhibitory role.[87]

The Voltage-gated Ion Channels

Sodium Channels

Nav channels are opened, once a threshold has been reached in the primary afferent. The resulting influx of extracellular sodium ions down their electrochemical gradient brings about membrane depolarization and propagation of an action potential from the periphery to the dorsal horn and beyond. Clearly, a decrease in the threshold of these channels by activation and an increase in their number will increase the rate at which action potentials are formed and transmitted, increasing pain sensitivity and intensity.

Nav channels exist in a number of different isoforms. Data collected from human and transgenic mice studies have suggested that Nav1.3, Nav1.7, Nav1.8, and Nav1.9 have differential roles in peripheral and central sensitization and inflammatory and neuropathic pain. Nav1.8 and Nav1.9 are expressed exclusively in nociceptive neurons.

Nav1.3 expression increases in the DRG following primary afferent injury[88] and in the second order neurons following spinal injury.[89] However, knockdowns only inhibited hypersensitivity following spinal injury, suggesting a more significant role in central sensitization in neuropathic pain.[89]

Nav1.7 is preferentially expressed in DRG and sympathetic ganglion and is activated close to the resting potential; therefore, can move the membrane potential toward threshold on activation. In humans, a mutation of the gene encoding Nav1.7 causing gain of function produces severe burning pain (eyrthromelagia), and one causing loss of function leads to insensitivity to pain altogether.[90] Nav1.7 knockout mice demonstrate hyposensitivity to innocuous mechanical and thermal stimuli in inflammatory[91] but not neuropathic pain.[92] Nav1.7 appears to be activated by PKC and upregulated by a p38 mitogen kinase mediated pathway processes initiated by binding of proinflamatory cytokines.[93] Binding of opioids to δ-receptors decreases PKC and p38 activity with a resultant reduction in Nav1.7 expression.[93]

Nav1.8 contributes significantly to the DRG action potential,[94] hence, increased sensitivity increases neural excitability. Nav1.8 knockout mice demonstrate decreased sensitivity to noxious mechanical and cold stimuli in inflammatory pain,[95] and Nav1.8 knockdown reversed neuropathic pain.[96] Nav1.8 is activated by PKA and PKC mediated phosphorylation. This is initiated by the neuropetides, CGRP (PKA and PKC)[97] and substance P (PKC),[98] and by PGE2 (PKC facilitating PKA mediated activation),[99] all released in response to nerve injury and inflammation.

Nav1.9 is active at the resting potential. Therefore, increasing opening leads to a rise in the potential, increasing neuronal excitability. Nav1.9 knockout mice demonstrated decreased thermal but not mechanical hypersensitivity in inflammatory models.[100] They also have decreased thermal hypersensitivity in response to injection of inflammatory mediators (PGE2, bradykinin, and IL-1β but not NGF) suggesting that Nav1.9 has a role in facilitating the effects of these mediators.[100] Activation of Nav1.9, like 1.8, results from phosphorylation mediated by PKC and PKA.[100] Nav1.9 knockouts do not have reduced excitatability in neuropathic pain models,[100] suggesting that role of Nav1.9 is limited to inflammatory persistent pain.

Currently, Nav channels are targeted nonspecifically, utilizing local anesthetic compounds and the anticonvulsants, such as carbamazepine or lamotrigine, but the global effects on membrane excitability narrows their therapeutic range. This is circumvented in the case of local anesthetics with topical application, but the area covered is limited by practicality and potential systemic toxicity. However, isoform specific antagonists (Nav1.7-NeP1 and Nav1.8-A-887826) are being studied in rodent models of neuropathic pain.[101,102] In addition, tricyclic antidepressants (TCAs) and serotonin uptake inhibitors also antagonize Nav1.7, TCAs at therapeutic doses, which may contribute to their antihyperalgesic efficacy.[103]

Potassium Channels

Voltage-gated potassium (Kv) channels also have a significant role in membrane excitability and nociceptive transmission.[104] Resting membrane potential is

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