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A brief comparison of the pathophysiology of inflammatory versus neuropathic pain

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Abstract

Purpose of review—The aetiologies of inflammatory pain and neuropathic pain are fundamentally different. There are, however, common mechanisms underlying the generation of each pain state. We will discuss some specific elements observed in both tissue and nerve injury pain states and consider the hypothesis that these two states actually demonstrate a convergence over time.

Recent findings—The increased pain sensation following tissue and nerve injury results from several mechanisms, including altered ion channel expression in DRG neurons, enhanced dorsal horn glutamate release from primary afferents, enhanced glutamate receptor function in second order neurons, disinhibition in the dorsal horn and glia cell activation. The role of specific subtypes of receptors, ion channels and glutamate transporters is revealed at peripheral and central sites. Importantly over time, a number of changes, in the dorsal root ganglion and in dorsal horn observed after tissue injury resemble changes observed after nerve injury.

Summary—Recognition of mechanisms common to both inflammatory pain and neuropathic pain might shed light on the understanding of the transition from acute pain to persistent pain.

Keywords

tissue injury; nerve injury; DRG; dorsal horn

Introduction

Heuristically, the pain experience has been divided into three principal categories based on the initiating conditions and the anticipated underlying mechanisms: Acute nociception, post-tissue injury/inflammation and post-nerve injury.

1. Acute nociception

Acute (transient) high intensity stimuli yield a somatotopically limited pain sensation that resolves upon the removal of the stimuli. The acute pain sensation is crucial to survival (witness the perilous existence of those who have no such acute sensation [1]). The encoding of the stimulus involves specific activation of subpopulations of fast-conducting, lightly

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myelinated (A δ) and slow-conducting, unmyelinated (C) fibers which are endowed with their response property by virtue of specific channels expressed on their terminals. This acute afferent traffic leads to activation of supraspinally projecting dorsal horn neurons, the frequency of their activation being dependent upon the frequency of afferent input and accordingly stimulus intensity.

2. Tissue injury

Tissue injury arising from ongoing exposure to high-intensity stimuli leads to a pain sensation continuing beyond the removal of the originating stimulus. There is, in addition, an enhanced sensitivity to otherwise modestly aversive stimuli applied to the injured tissue (hyperalgesia). Typically such pain resolves in parallel with resolution of the injury state (e.g. healing). At the peripheral terminal, injury/inflammation leads to an innate immune cascade yielding release of active factors from blood, local and migrating inflammatory cells and injured cells. These products initiate activity in C fibers through eponymous receptors located on the afferent terminal and sensitize these terminals. At the level of the spinal dorsal horn, ongoing afferent traffic leads to initiation of a robust facilitation of dorsal horn output. The systems underlying this spinal facilitation include:

a. enhanced postsynaptic transmission—i) Enablement of the NMDA receptor by loss of the magnesium block [2].

ii) Increased trafficking of AMPA receptor subunits, particular those which are calcium-permeable [3].

iii) Activation of kinases which phosphorylate membrane channels and receptors to enable their activity [4].

iv) Activation of kinases which activate intracellular enzymes such as phospholipase A2 (leading to increased formation of lipid metabolites) [5-6]

b. Spinobulbospinal pathway—Afferent input activates caudal midline raphe-spinal serotonergic neurons which terminate in dorsal horn neurons to facilitate the activity in deep dorsal horn projection systems [7-8].

c. Loss of local inhibition—Local dorsal horn neuronal excitability is under the tonic control of local inhibitory GABAergic and glycinergic interneurons. Loss of this inhibitory control leads to potent allodynia [9]. Locally released prostaglandins have been shown to inhibit the function of glycine receptors, leading to a loss of local inhibition [10].

d. Local non neuronal cell systems—Peripheral inflammation leads to both acute and chronic indices of activation of spinal microglia and astrocytes. Activation of these cell systems have been shown to release a variety of pro-excitatory neurohormones including cytokines, chemokines, ATP and PAR agonists [11].

e. Migration of non-neuronal inflammatory cells into the DRG—Peripheral inflammation results in the appearance of macrophages in the DRG, but not the spinal cord [12].

3. Peripheral nerve injury

Injury to the peripheral nerve leads to a pain state with persistency and components of hyperalgesia and allodynia (aversive sensation generated by an otherwise innocuous stimulus) referred to the distribution of the injured nerve. In these instances, evidence

suggests that the ongoing sensations reflect the activation of small afferent traffic which arises from the distal spouting of the injured axons and from the DRG of the injured axon. The peripheral and spinal mechanisms underlying this increased spontaneous activity are broadly summarized in terms of:

a. Altered channel expression—Increased expression of a variety of sodium channels in the neuroma and in the DRG [13], reduced expression of potassium channels [14-15] and increased expression of $\alpha_2\delta_1$, the auxiliary subunit of voltage-gated calcium channels [16-17] has been noted.

b. Upregulation of markers for neuronal injury—Such markers include GAP43 [18] and Activating transcription factor 3 (ATF3) [19].

c. Increased expression of neuroma and DRG receptors—Receptors that are activated by products in the altered milieu have been shown including those for TNF α , bradykinin, NGF and catecholamines [20-23].

d. Migration of nonneuronal inflammatory cells into the DRG—After nerve injury, increased macrophages and neutrophils have been shown in the DRG [24-25].

e. Activity-induced facilitation—The ongoing afferent traffic is believed to contribute importantly to the initiation of a central sensitization state with several components including activation of the NMAD receptors and increased AMPA subunit expression [26-27].

f. Loss of inhibition—Nerve injury leads to a change in the dorsal horn Cl⁻ transporters which in turn leads to a shift in the Cl⁻ equilibrium potential such that increasing Cl⁻ conductance will lead to a depolarization of the dorsal horn neurons rather than an inhibitory hyperpolarization [28].

g . Spinobulbospinal facilitatory pathways—As noted above, spinobulbospinal pathways lead to the activation through the caudal midline raphe of serotonergic projections, which terminate in dorsal horn neurons to activate dorsal horn projection systems. Lesions of this system at the level of the ascending neurons [29] or at the descending link [30-32] abolish allodynia.

h. Activation of non-neuronal cells—After nerve injury there are trophic changes in the appearance of microglia and astrocytes, suggesting increased activity of non-neuronal cells [11].

i. Migration of non-neuronal inflammatory cells into dorsal horn—Peripheral nerve injury produces segmentally organized disruption of the blood brain barrier [33] and the influx of T cells and macrophages [34].

Separation of tissue vs. neuropathic injury pain phenotypes

Based on the preceding overview, it can be seen that following peripheral tissue and nerve injury a variety of mechanisms are brought into play that alter nociceptive processing. Three characteristics would seem to firmly distinguish the two pain states.

a. Resolution of pain

Tissue injury-associated pain typically improves as a function of “healing” and resolution of the inflammation. In contrast neuropathic pain frequently does not show such reversal and persists despite an evident resolution of the injury with which the sensation is associated. We would note however that increasingly, there is an appreciation that in some instances the inflammatory/injury state may resolve but a component of pain persists [35]. In humans a significant percentage of patients show this failure to resolve their pain after a variety of interventions including soft tissue resection [36], herniorrhaphy [37] and joint repair [35]. In animals chronic inflammatory states may demonstrate a resolution of inflammation with a persistent allodynia [38].

b. Role of low threshold afferent

The neuropathic allodynia almost certainly reflects the activation of A β afferents in addition to an element of sensitized C-fibers [39].

c. Pharmacology

As shown in table 1, in preclinical models, inflammatory hyperalgesia are frequently sensitive to agents such as NSAIDs and opiates whereas neuropathic pain states are not. It should be noted that this difference does not reflect upon a peripheral pharmacology as similar results are observed after spinal delivery. Interestingly, many of the agents effective in nerve injury models such as NMDA antagonists and gabapentinoids also show efficacy in tissue injury models.

Comparison of tissue vs. neuropathic injury pain mechanisms

In the following sections we would like to discuss some specific elements observed in both tissue and nerve injury pain states and consider the hypothesis that these two states actually demonstrated a convergence over time (Figure 1).

a. TNF-alpha

TNF α is a key regulator of the inflammatory response and is involved in increased production of proalgesic agents. Etanercept, a TNF α inhibitor, has been effective for the treatment of rheumatoid arthritis and other inflammatory diseases [40]. Injection of TNF α into sciatic nerve elicits hyperalgesia and allodynia that last for days, which is associated with nerve edema, Schwann cell injury and macrophage activation [41]. It was later shown that topically applied TNF α induced ectopic firing in C and A-delta fibers [42]. Local TNF α also lowered the mechanical threshold of C-nociceptors and caused ongoing activity in some C nociceptors [43]. The level of TNF α in DRG is increased after peripheral nerve injury [44], as well as the two TNF α receptors, TNFR1 and TNFR2 [22]. Normally expressed in mast cells, TNF α following nerve injury is thought to be induced in infiltrating ED1⁺ macrophages in a TLR2-dependent fashion [45] and Schwann cells [46]. In SNL rats, exogenously applied TNF α is able to increase the sensitivity of both injured and adjacent uninjured DRG neurons. Injured DRG neurons not only respond to TNF α at much lower concentrations but also exhibit enhanced discharges, a mechanism likely responsible for allodynia and spontaneous pain behaviour [47]. TNF α blockade prevented or reversed neuropathic pain in a number of animal models [48-49]. Recent work has shown that epidural TNF α block relieves *sciatica* pain in man [50].

b. Voltage-gated sodium channels

VGSCs control the propagation of nerve impulses and are therefore essential for the excitability of neurons. Sodium channel blockers, such as local anesthetics, are a mainstay

of pain medicine. Several VGSC members are implicated in persistent pain, including Nav1.3, Nav1.7 and Nav1.8 [13, 51]. Mutations of Nav1.7 are linked to several rare human pain disorders including erythromelalgia (gain of function) [52] and congenital insensitivity to pain (non-sense mutation, loss of function) [1]. Nav1.7 is highly expressed in nociceptors. An increased level of Nav1.7 was seen following peripheral inflammation, mediated by COX-dependent mechanisms [53]. Disrupting Nav1.7 in nociceptors attenuated pain hypersensitivity in several inflammatory pain models [54]. Interestingly, neuropathic pain developed normally in those Nav1.7 knockout mice [55]. It should be noted the knockout of Nav1.7 was limited to nociceptors that co-express Nav1.8. It is therefore possible that other groups of Nav1.7 primary afferents or other sodium channels contribute to neuropathic pain.

Nav1.8 is selectively expressed in nociceptors. Rapid increase in Nav1.8 level is induced by a number of inflammatory mediators [51] and disrupting Nav1.8 abolished inflammatory pain [55]. Certain types of neuropathic pain, however, are preserved not only in animals with Nav1.8 knockout but also in animals with the Nav1.8-expressing nociceptors ablated [56], suggesting there are distinct pathways governing inflammatory vs. neuropathic pain at the primary afferent level.

Transection of the L5 ventral root produces prolonged allodynia [57]. Recent studies demonstrated that Nav1.8 is upregulated in the uninjured L4 and L5 DRG after L5 ventral root transection [58-59]. The increased membrane expression of Nav1.8 leads to spontaneous repetitive discharge, a mechanism for spontaneous pain. Small molecules that selectively inhibit Nav1.7 and/or Nav1.8 for the treatment of neuropathic pain are under active investigation.

c. Voltage-gated calcium channels

VGCCs are critical in controlling neurotransmitter release. Several VGCCs are detected in DRG neurons and implicated in pain. Inhibitors for N-, T- and L-type VGCCs are used clinically to alleviate neuropathic pain [60]. The VGCC accessory subunit $\alpha 2\delta 1$, the main target for gabapentin and pregabalin, is upregulated in injured DRG neurons [16-17]. $\alpha 2\delta 1$ facilitates trafficking of Cav2.1 into the cell membrane [61], thereby modulating excitability of DRG neurons. The role of $\alpha 2\delta 1$ in neuropathic pain is supported by the efficacy of gabapentin and pregabalin in the treatment of neuropathic pain patients, as well as preclinical findings that intrathecal antisense oligonucleotides against the $\alpha 2\delta 1$ subunit block neuropathic pain [62-64]. Changes in $\alpha 2\delta 1$ expression are not reported in inflammatory pain. Gabapentin, however, does inhibit inflammatory pain in preclinical models, suggesting a mechanism independent of one requiring increased $\alpha 2\delta 1$ subunit expression [38, 65].

d. Altered gene expression in DRG neurons

Nerve lesion induces expression of genes that are related to regeneration, such as ATF3 [19]. Overexpression of ATF3 promotes neurite outgrowth in culture DRG neurons [66]. In transgenic mice that constitutively express ATF3 in the DRG neurons, the rate of nerve regeneration following injury is significantly increased [67]. There is a certain degree of correlation between the type of stimuli and the subpopulation of sensory neurons that show ATF3 expression. Thus hindpaw injections of capsaicin, mustard oil or menthol induced expression of ATF3 in DRG neurons that express the expected TRP channel subtypes [68]. The induction of ATF3 seems rather selective for compounds or insults that may lead to nerve injury. Agents that cause inflammation, such as carrageenan or CFA, do not induce ATF3 expression [68], suggesting nerve injury, rather than the mere increased activity is required. Using DRG ATF3 as a marker, a role of nerve injury has been revealed in persistent pain following back skin incision [69]. DRG ATF3 expression was also noticed in

the K/BxN mouse arthritis model, but only in the late phase when the peripherally inflammation was fully resolved [38]. This “late” pain is associated with a loss of response to NSAIDs, suggesting the pain of inflammatory origin evolved into a condition that is similar to neuropathic pain. Revealing the signaling events surrounding ATF3 activation might hold the key to the understanding of the transition from acute to chronic pain.

e. VGLUT and central terminal glutamate release

Glutamate is the major excitatory neurotransmitter in the CNS. Glutamatergic activity is regulated by removal of glutamate from the synaptic cleft by both neurons and astrocytes [70]. Once in the cell, vesicular glutamate transporters (VGLUT1–VGLUT3) mediate glutamate uptake into vesicles from which glutamate can be released in a calcium-dependent fashion [71]. Null mutation of VGLUT1 and VGLUT2 are lethal [72–74]. Heterozygote mice are viable and relatively normal. While heterozygous VGLUT1 mice did not show significant changes in their pain behaviors, global reduction of VGLUT2 attenuated some aspects of neuropathic pain [75]. Further studies were carried out in mice with conditional knockout of VGLUT2 in DRG neuron subpopulations defined by the expression of peripherin, Nav1.8 and tyrosine hydroxylase (Th). All of these conditional knockout animals showed deficits to some degree in acute and chronic pain, although the phenotypes do not completely overlap [76–78]. In all cases, attenuated nociception is associated with reduced firing of superficial dorsal horn neurons or c-fos expression, confirming a key role for glutamate release from the central terminals.

The role of VGLUT3 is less understood. VGLUT3 is expressed in a small group of DRG neurons, with their central afferents terminating in the superficial layer of spinal dorsal horn. VGLUT3 knockout animals do not develop mechanical hypersensitivity in models of inflammatory pain and neuropathic pain, while noxious heat sensation is largely intact. In addition, VGLUT3 appears to be primarily responsible for transport of glutamate into astrocyte vesicles [79], which can subsequently be released by astrocyte activation.

f. Post synaptic activation

Release of glutamate in the spinal dorsal horn leads to activation of a variety of ionotropic receptors. The importance of this release is indicated by the fact that AMPA receptor blockade results in a virtual complete block of acute post-synaptic excitation while blockade of the NMDA receptor has little effect upon acute excitation, but can markedly diminish the initiation of the enhanced response of spinal neurons to repetitive small afferent input (e.g. wind up) [27].

In response to peripheral inflammation and increased primary afferent traffic, synaptic efficacy in the spinal cord dorsal horn is strengthened, which in part results from the enhanced function of postsynaptic glutamate receptors [27]. For example, intraplantar CFA promotes trafficking of NR2B to synapses in the spinal cord dorsal horn [80]. NMDA receptors containing NR2B have slower decay kinetics therefore allow more Ca^{2+} influx, leading to hyperactivity of second-order neurons. Changes in channel properties are extensively studied for AMPA receptors. Kopach et al. showed that extrasynaptic GluR1 containing AMPARs is significantly increased in the tonically firing substantia gelatinosa neurons [81]. Choi et al. showed that the trafficking of GluR1 to neuron membrane is $\text{TNF}\alpha$ dependent [82]. GluR1 containing AMPARs are permeable to Ca^{2+} . Thus, the increase of GluR1 at synaptic sites enhances Ca^{2+} influx and the excitability of dorsal horn neurons.

g. Disinhibition

Dorsal horn nociceptive neurons are under powerful inhibitory control. Intrathecal strychnine (glycine receptor antagonist) or bicuculline (GABA A receptor antagonist)

evokes immediate tactile allodynia, but had no effect upon thermal escape thresholds [9], suggesting that tonic or evoked glycinergic or GABAergic inhibition in the spinal cord is crucial to the encoding of low threshold mechanical (tactile) stimuli as a non-aversive stimulus. GABA and glycinergic interneurons have indeed been shown to exert a potent regulation of large primary afferent terminal and postsynaptic excitability through their respective receptors, which are Cl^- ionophores. Loss of this GABAergic/glycinergic inhibition would thus permit an enhanced activation, resulting from i) decreased numbers or content of glycine and/or GABA [83-84], ii) attenuated function or lowered expression of glycine and/or GABA receptors and/or iii) GABAergic excitation. For dorsal horn neurons, the equilibrium potential of Cl^- is such that the opening of GABA_A receptors or glycine channels causes an influx of Cl^- and hyperpolarization. Reduced activity of K^+-Cl^- cotransporter (KCC) and/or enhanced activity of $\text{Na}^+-\text{K}^+-\text{Cl}^-$ cotransporter (NKCC) could lead to increased intracellular Cl^- , therefore the opening of GABA_A channel induces depolarization and excitation of dorsal horn nociceptive neurons. This mechanism is implicated in both inflammatory pain and neuropathic pain [85]. Reduced spinal expression of KCC2 is noticed following intraplantar formalin [86] or CFA [87], as well as nerve injury [28]. Fast phosphorylation of dorsal horn NKCC1 is seen within 10 min after intracolonic capsaicin injection [88]. The phosphorylation likely promotes membrane trafficking of NKCC1 and might play a role in referred mechanical hyperalgesia. Intraplantar capsaicin produced a significant enhancement in spike frequency in both wide dynamic range (WDR) and nociceptive specific neurons in dorsal horn. Spinal blockade of NKCC1 normalized the spike frequency to baseline levels, suggesting that NKCC1 plays a key role in the sensitization of dorsal horn neurons [89].

h. Involvement of spinal glia

It is increasingly recognized that glia, especially microglia play important roles in the generation of chronic pain [90-92]. A number of factors contribute to dorsal horn microglia activation following tissue/nerve injury, including $\text{TNF}\alpha$, PGE_2 , ATP and IL6. Mice deficient in PGE_2 production have impaired dorsal horn activation of microglia and do not exhibit mechanical allodynia after peripheral nerve injury [93]. This study revealed that PGE_2 acts through both EP1 and EP2 to retain microglia in the central terminal of primary afferents. IL6, a proinflammatory cytokine, is induced in the dorsal horn following nerve injury and is involved in the early activation of the JAK/STAT3 pathway [94]. JAK/STAT3 in turn stimulates the production of more IL6 and CC chemokine ligand CCL2. In addition, IL6 activates microglial p38 MAPK pathway-mediated expression of fractalkine receptor CX3CR1 [95], thereby promoting the interaction between dorsal horn neurons and microglia. Proinflammatory cytokines release from activated microglia modulates neuronal synaptic transmission. $\text{TNF}\alpha$, for example, rapidly inhibited spontaneous action potentials in GABAergic neurons in a p38 dependent fashion, leading to disinhibition [96].

In addition to its role in cytokine production, activated microglia could assume an amoeboid shape and act similar to a macrophage. Following peripheral nerve injury, microglia in lamina II-III were shown to engulf both injured and uninjured myelinated axons, a phenomenon not observed in the normal dorsal horn [97]. The engulfment of axons likely induces injuries to spinal cord neurons, as indicated by the dorsal horn expression of ATF3. Thus microglia activation may introduce central pain components to an existing peripheral neuropathic pain.

Conclusion

There is no doubt that inflammatory pain and neuropathic pain share common mechanisms, although the time course and relative contribution of each of these mechanisms might be different. A more precise depiction of these differences is critical in providing the rationale

for a timely intervention, which might prevent the transition from acute pain to a persistent, chronic state. It becomes clear that a successful approach is likely to involve not only analgesics, but also means that may modify the progression of pain as a disease.

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Abbreviations

NMDA	N-methyl-D-aspartate
AMPA	2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid
DRG	dorsal root ganglion
VGLUT	vesicular glutamate transporter
NSAIDs	nonsteroidal anti-inflammatory drugs
COX	cyclooxygenase
MOR	mu opioid receptor
VGSC	voltage-gated sodium channel
VGCC	voltage-gated calcium channel
TNFα	tumor necrosis factor-alpha
GABA	γ -aminobutyric acid
MAPK	mitogen-activated protein kinases
CNS	central nervous system
PAR	protease-activated receptor
GAP43	growth associated protein 43
NGF	nerve growth factor
NK1R	neurokinin 1 receptor
TLR	Toll-like receptors
CCI	chronic constriction injury
PGE2	prostaglandin E2
ATP	adenosine-5'-triphosphate
IL6	interleukin 6
JAK/STAT3	Janus kinase/signal transducer and activator of transcription
CX3CR1	CX3C chemokine receptor 1

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KEY POINTS

1. Inflammatory pain and neuropathic pain can be distinguished from the following characteristics: resolution of pain, involvement of A β afferent and pharmacology.
2. Mechanisms common to both inflammatory and neuropathic pain include altered expression of cytokines, cytokine receptors and VGSCs in the DRG, enhanced glutamate release and receptor functions, disinhibition and glia activation and invasion in the spinal dorsal horn.
3. Nerve injury marker ATF3 is observed in the DRG neurons following prolonged peripheral inflammation, suggesting the pain of inflammatory origin may evolve into a condition that resembles neuropathic pain.

Mechanisms Leading to Persistent Pain Following Tissue Injury or Nerve Injury

Fig 1. Mechanisms mediating persistent pain following tissue injury or nerve injury

Following tissue injury or nerve injury, pathological changes that might lead to persistent pain in the DRG (1) and the spinal cord dorsal horn (2). Common mechanisms are listed in the gray boxes. See text for details. ATF3, cyclic AMP-dependent transcription factor; TNF, tumor necrosis factor; TNFr, tumor necrosis factor receptor.

Table 1

Analgesic pharmacology of nerve and tissue injury pain states

Drugs	Target(s)	Site of action	Efficacy	
			Inflammatory hyperalgesia	Neuropathic Allodynia
NSAIDs	COX	Peripheral	+	–
NMDA antagonists	NMDAR	Dorsal horn	+	+
Mu-opiates	MOR	Central terminal, dorsal horn neurons	+	+/-
Gabapentinoid	$\alpha 2\delta$	Central terminal	+	+
anticonvulsants	VGSC	peripheral	+	+
TNF α blocker	TNFr	Peripheral	+	+/-