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Review Article

The Known Biology of Neuropathic Pain and Its Relevance to Pain Management

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ABSTRACT: Patients with neuropathic pain are heterogeneous in pathophysiology, etiology, and clinical presentation. Signs and symptoms are determined by the nature of the injury and factors such as genetics, sex, prior injury, age, culture, and environment. Basic science has provided general information about pain etiology by studying the consequences of peripheral injury in rodent models. This is associated with the release of inflammatory cytokines, chemokines, and growth factors that sensitize sensory nerve endings, alter gene expression, promote post-translational modification of proteins, and alter ion channel function. This leads to spontaneous activity in primary afferent neurons that is crucial for the onset and persistence of pain and the release of secondary mediators such as colony-stimulating factor 1 from primary afferent terminals. These promote the release of tertiary mediators such as brain-derived neurotrophic factor and interleukin-1β from microglia and astrocytes. Tertiary mediators facilitate the transmission of nociceptive information at the spinal, thalamic, and cortical levels. For the most part, these findings have failed to identify new therapeutic approaches. More recent basic science has better mirrored the clinical situation by addressing the pathophysiology associated with specific types of injury, refinement of methodology, and attention to various contributory factors such as sex. Improved quantification of sensory profiles in each patient and their distribution into defined clusters may improve translation between basic science and clinical practice. If such quantification can be traced back to cellular and molecular aspects of pathophysiology, this may lead to personalized medicine approaches that dictate a rational therapeutic approach for each individual.

RÉSUMÉ : Nos connaissances actuelles en biologie en ce qui concerne la douleur neuropathique et leur pertinence pour la prise en charge de la douleur. Les patients souffrant de douleurs neuropathiques sont hétérogènes en termes de pathophysiologie, d'étiologie et de présentation clinique. Leurs signes cliniques et leurs symptômes sont déterminés par la nature de leur lésion ainsi que par des facteurs tels que la génétique, le sexe, une lésion antérieure, l'âge, la culture et l'environnement. À l'aide de modèles appliqués à des rongeurs, nos connaissances scientifiques fondamentales ont fourni des éléments généraux d'information sur l'étiologie de la douleur en étudiant les conséquences de lésions périphériques. Un tel phénomène est associé à la libération de cytokines pro-inflammatoires, de chimiokines et de facteurs de croissance qui sensibilisent les terminaisons nerveuses sensorielles, modifient l'expression génétique, favorisent la modification post-traductionnelle des protéines et altèrent la fonction des canaux ioniques. Cela conduit en retour à une activité spontanée dans les neurones afférents primaires, laquelle est cruciale dans l'apparition et la persistance de la douleur et la libération de médiateurs secondaires, par exemple le récepteur de « facteur de stimulation des colonies 1 » à partir des terminaisons afférentes primaires. Ces dernières favorisent par ailleurs la libération de médiateurs tertiaires tels que le facteur neurotrophique dérivé du cerveau (FNDC) et l'interleukine-1β par la microglie et les astrocytes. Les médiateurs tertiaires facilitent aussi la transmission des informations nociceptives aux niveaux spinal, thalamique et cortical. Dans l'ensemble, ces découvertes n'ont pas permis d'identifier de nouvelles approches thérapeutiques. Cela dit, les avancées plus récentes de la science fondamentale reflètent mieux la situation clinique des patients en abordant la ou les pathophysiologies associées à des types spécifiques de lésions, en affinant la méthodologie employée et en prêtant attention à divers facteurs contributifs, par exemple le sexe. Une meilleure quantification du profil sensoriel de chaque patient et leur répartition en groupes définis peuvent ainsi améliorer le transfert entre les connaissances fondamentales de la science et la pratique clinique. Si cette quantification parvient à remonter jusqu'aux aspects cellulaires et moléculaires de la physiopathologie, cela pourrait conduire à des approches médicales personnalisées qui dictent une approche thérapeutique rationnelle pour chaque individu.

Keywords: Neurogenic neuroinflammation; Allodynia; Dorsal horn; Dorsal root ganglia; Central sensitization; Neuropathy; Nerve injury; Neuroimmunology; Brain-derived neurotrophic factor; Quantitative sensory testing

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Introduction

The signs and symptoms of neuropathic pain in each individual patient are strongly dependent on variables such as sex, age, ethnicity, inherited genetic predisposition, intestinal microbiome, prior neonatal injury, personality variables, and cultural and environmental factors.[1–5] This heterogeneity of presentation also reflects the association of neuropathic pain with a diverse set of maladies. These include peripheral nerve trauma, brain or spinal cord injury, fibromyalgia, multiple sclerosis, spinal, cortical or brain stem cord stroke, post herpetic and trigeminal neuralgia, migraine, osteoarthritis, rheumatoid arthritis, autoimmune disease, complex regional pain syndromes I and II, viral infections such as HIV and COVID-19 and neuropathies associated with diabetes, chemotherapy, and cancer itself.[6]

Signs and symptoms include hyperalgesia, mechanical, or cold-induced allodynia, bouts of spontaneous "electric shock like" pain and sometimes the persistent burning pain of causalgia[6] Some patients experience sensory disturbances. These may involve paresthesias, described as a crawling sensation, pricking or tingling[7] or *anesthesia dolorosa* where the area of injury is painful yet insensitive to touch.[8] Neuropathic pain is frequently intractable, relatively insensitive to the action of opioids[9,10] and may present with comorbidities such as anxiety, irritability, sleep disorders, depression, and/or sensory abnormalities.[7,11] Despite intensive efforts to find new drugs and targets over the past 30 years, the urgent need to find new treatments persists.[6,9,10,12] Most of the current understanding is derived from peripheral nerve injury models in rodents. In most cases, the spared nerve injury (SNI) or chronic constriction injury (CCI) models are used.[13]

This review will overview the current understanding of pain induced in animal models by peripheral nerve injury. In view of the recognized knowledge gap between these basic science results and the various signs and symptoms and/or pain phenotypes seen in patients,[12] a brief outline of clinical and basic science strategies that seek to bridge this gap will be presented.

Nerve Injury, Wallarian Degeneration, and Primary Mediators

Following injury, Wallerian degeneration of severed axons is associated with neutrophil, macrophage, and T-lymphocyte invasion as well as activation of Schwann cells, fibroblasts, mast cells, keratinocytes, and epithelial cells.[14–16] Once activated, these immunocompetent cells generate and release pro-inflammatory primary mediators. These include tumor necrosis factor (TNF-α),[14,17] interleukins 1β,15,17 and 18 (IL-1β, IL-15, IL-17, and IL-18),[14,18–21] nerve growth factor,[14,22] monocyte chemoattractant protein 1 (MCP-1/CCL-2),[23] chemokine (C-X-C motif) ligands 1 (CXCL-1)[14,24] and 12 (CXCL-12),[25] histamine, prostaglandins, serotonin, and substance P[14,26,27] as well as the secreted glycoproteins Wnt3a (wingless-type mammary tumor virus integration site family member 3a) and Wnt5a.[28]

Structural Remodeling of Injured Peripheral Nerves

Following SNI of rodent peripheral nerves, degeneration of the axons of low threshold non-nociceptive afferents can lead to loss of sensation. Peripheral nociceptors then sprout into territories that were previously occupied by low threshold afferents. These nociceptors are transformed to exhibit a low activation threshold so that mild tactile stimulation now produces mechanical allodynia.[29]

In many cases, injury also provokes the sprouting of perivascular sympathetic fibers so that they interact and excite sensory nerve terminals and DRG cell bodies.[30,31] These processes are especially relevant to the etiology of complex regional pain syndrome II.[32]

Injury-Induced Peripheral Sensitization, the Importance of Spontaneous Activity, and the Generation of Secondary Mediators

Immune cell-derived primary mediators sensitize peripheral nerve endings, axons, and cell bodies of primary afferents.[14] Mediators also promote plasma extravasation and increase the permeability of the blood–brain barrier[33] and the blood–nerve barrier in the periphery.[34] This and the chemoattractant profiles of various mediators facilitate the recruitment of immunocompetent leucocytes and lymphocytes to the site of injury.[15,20] These myeloid and lymphoid cells themselves release a host of cytokines and chemokines thereby instigating a positive feedback process in the initiation and maintenance of neuroinflammation and pain. Neuroinflammation is defined as activation of the brain's innate immune system in response to an inflammatory challenge.[35,36]

Satellite glial cells and resident macrophages in DRG[37–39] represent yet another source of inflammatory mediators. The actions of primary mediators such as IL-1β and TNF-α on DRG neurons culminate in marked changes in genes coding for neuropeptides, cytokines, chemokines, receptors, ion channels, signal transduction molecules, and synaptic vesicle proteins.[40,41] Some of these gene products also function as secondary mediators that are released and effect the transfer of information between damaged peripheral nerves and various cell types in the spinal dorsal horn.[18]

Primary mediators also control the expression of long non-coding RNA's[42] and microRNA's in DRG. The latter are also upregulated by nerve injury[6] and post-transcriptionally regulate the protein expression of hundreds of genes in a sequence-specific manner.[43] Transfer of microRNAs between cell types may be brought about by the release and uptake of exosomes.[44]

Importantly, altered function of ion channels as a result of the action of primary mediators leads to increased excitability of primary afferent neurons[45–49] and the generation of stimulus-independent spontaneous activity. This incessant spontaneous activity in primary afferents is absolutely crucial for the onset and persistence of pain.[50–53] This is illustrated by the effectiveness of topically applied lidocaine in the clinic.[54] Altered ion channel function and peripheral hyperexcitability may even be involved in spinal cord injury[55] and central post-stroke pain.[56] Although $Na_v1.7$, $K_v7.2$, $Ca_v2.2$, $Ca_v3.2$, and HCN2 channels have emerged as potential therapeutic targets for drug development, with the notable exception of gabapentinoid action on voltage-gated Ca^{2+} channels,[9] pharmacological manipulation of these channels has failed to identify new therapeutic approaches.[57]

The observation that peripherally generated pain is often not suppressed by rhizotomy[58] seems at odds with the idea that stimulus-independent spontaneous activity is required for pain maintenance. It is possible, however, that pain seen after rhizotomy is related to deafferentation. This deafferentation pain may replace that which previously resulted from ectopic primary afferent activity.[58]

As would be expected, the population of ion channels affected by primary mediators is similar to that affected by peripheral nerve injury[45,47,59] and in animal models, blockade of the actions of primary mediators abrogates signs of injury-induced pain.[14,15,18,60–63]

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In general however, attempts to block the action of inflammatory mediators to limit neuropathic pain in the clinic have met with limited success.[64]

Bidirectional Signalling between the Nervous and Immune Systems and "Neurogenic Neuroinflammation"

The relationship between immune cells and neurons is bidirectional. In addition to the well-documented actions of immune mediators on neurons,[18,45–48,65–67] neuronal activity has a direct effect on immune cells.[68–72] This "neurogenic neuroinflammation"[73] is brought about by the release of neuropeptides and glutamate from primary afferents and their interaction with their cognate receptors on immune cells, astrocytes, and microglia.[72,74]

Actions of Secondary Mediators and Transfer of Information from the Periphery to the Spinal Cord

Most secondary mediators are released from primary afferent terminals. Substances such as colony-stimulating factor 1 (CSF-1), the chemokines CCL-21, CXCL-12, and Wnt3a and Wnt5a[6,18,28,75–78] activate their cognate receptors on spinal microglia and/or astrocytes and alter their properties. Activated glia thereby detects and mount an enduring response to peripheral nerve injury. Spinal microglia are affected in male rodents[77] whereas invading macrophages and adaptive immune cells such as T-lymphocytes are involved in females.[79–81] CCL-21 and CXCL-12 signal to activate astrocytes.[78,82] The inflammatory mediator, IFN-γ is increased in spinal cord following peripheral nerve injury[83] and this may originate from invading T-lymphocytes.

Generation and Release of Tertiary Mediators in the Dorsal Horn and Central Sensitizaton

Glial activation and proliferation leads to the generation and release of tertiary mediators such as BDNF, IL-1β, TNF-α, and IFN-γ.[18,84,85]

BDNF is released from microglia in response to the secondary mediators CSF-1[18,76,86,87] and/or Wnt3a.[88] BDNF release requires activation of P2X4 receptors by ATP.[9,89] As a mediator of the effect of nerve injury,[90–92] BDNF facilitates excitation[84,93–95] and attenuates inhibition in the superficial dorsal horn.[9,96] These changes, which lead to central sensitization, spontaneous activity, and the misprocessing of sensory information,[97–100] involve at least four cellular mechanisms.

Microglial-derived BDNF increases excitatory drive to excitatory dorsal horn neurons and inhibits that to inhibitory neurons by both presynaptic and postsynaptic mechanisms.[87,93,94] This altered synaptic activity is capable of increasing spontaneous action potential discharge in excitatory neurons while reducing it in inhibitory neurons.[93]

BDNF also enhances excitatory responses to N-methyl-d aspartate (NMDA) in rat spinal cord *in vitro*.[101] This may involve potentiation of the function of presynaptic NMDA receptors on primary afferent terminals[102] with a resultant increase in excitatory glutamatergic transmission. This may contribute to the effectiveness of the NMDA blocker, ketamine in some patients.[54]

Peripheral nerve injury reduces expression of the potassium-chloride exporter (KCC2) selectively in nociceptive dorsal horn neurons.[90,103] The resulting accumulation of intracellular Cl^- normally causes outward, inhibitory GABAergic synaptic currents mediated by Cl^- influx to become inward excitatory currents mediated by Cl^- efflux.[90] In male rats, this downregulation of KCC2 is mediated by BDNF.[104] Since the loss of GABAergic inhibition enables non-noxious Aβ fiber-mediated excitatory transmission to access the superficial spinal dorsal horn, this process contributes to the establishment of allodynia.[99]

Long-term potentiation (LTP) of synaptic transmission, sometimes known as "wind-up", contributes to central sensitization in the dorsal horn.[105,106] LTP of C-fibre responses is augmented by BDNF[107] and LTP induced by nerve stimulation is occluded by BDNF pretreatment.[108] The importance of these effects was recently underlined by the observation that spinal LTP as well as microglial activation and upregulation of BDNF are inhibited by antibodies to the secondary mediator CSF-1. This strongly implicates the CSF-1-microglia-BDNF axis[18] in the generation of spinal LTP.[109]

As already mentioned, in females, changes in sensory processing in the dorsal horn involve the invasion of macrophages and T-lymphocytes.[80,81] Yet as in males, this leads to attenuation of inhibition following the collapse of the Cl^- gradient.[110] In females, collapse of the Cl^- gradient is also brought about by the neuropeptide, CGRP[111] which is released from primary afferent terminals.[112]

IL-1β from microglia stimulates astrocytic production of both TNF-α and IL-1β itself[113] thereby amplifying the initial IL-1β signal. Spinal actions of IL-1β involve increases in excitatory synaptic transmission.[65,66] This may involve a reduction in the ability of astrocytes to take up glutamate as a result of internalization of the astrocytic glutamate transporter (EAAT2).[114]

TNF-α also augments excitatory transmission in the dorsal horn[18,66] as well as LTP by an action on glial cells.[115] Blockade of TNF-1 receptors attenuates neuropathic pain in male rodents but not in females.[116] Although anti-TNF antibodies and anti-TNF drugs such as thalidomide are available, none seem particularly useful in pain management.[117]

IFN-γ from invading T-lymphocytes induces both tactile allodynia and altered microglia function. Genetic ablation of the interferon receptor (IFN-γR) impairs nerve injury-evoked activation of ipsilateral microglia and tactile allodynia.[118] IFN-γ also increases dorsal horn excitability[119] and facilitates synaptic transmission between primary afferent C-fibres and Lamina 1 neurons via a microglial dependent mechanism.[120]

Failure to Resolve Chronic Neuroinflammation

All types of injury are capable of promoting inflammation and pain[121] and the interactions of inflammatory mediators with neurons, glia, immunocompetent leucocytes and lymphocytes, and macrophages[14] promote neuroinflammation. Since identified "off signals" actively suppress the classical signs of inflammation,[121,122] pain is usually short lasting or acute. The signals that actively resolve inflammation and pain include anti-inflammatory cytokines such as IL-10 and lipid-derived specialized pro-resolving mediators (SPMs).[123,124] Despite this, the neuroinflammation associated with neuropathic pain may not resolve, thereby promoting the transition from acute pain to chronic pain.[121] As already mentioned, spontaneous and ectopic activity in primary afferent fibers is crucial for the maintenance and persistence of signs of neuropathic pain.[50–53,56] Excessive neuronal activity releases glutamate and neuropeptides which interact with glia and immune cells to provoke the generation of inflammatory mediators.[73] It is possible that this incessant neurogenic neuroinflammation overcomes the resolution processes that normally terminate inflammation thereby contributing to the indefinite persistence of neuropathic pain.

In addition, the injury-induced structural changes in peripheral afferent[29] and sympathetic nerves[30,31] and in higher brain

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structures are almost certainly irreversible.[12] These enduring changes also contribute to the chronic nature of neuropathic pain.

Changes in Central Sensory Pathways in Higher Brain Regions

Cytokine/chemokine/growth factor/glial cell interactions are also involved in modulation of sensory information in the mesolimbic system,[125] thalamus, sensory cortex, nucleus accumbens, and amygdala.[125–127] Peripheral nerve injury promotes microglial activation in the contralateral thalamus, sensory cortex, and amygdala as would be expected from the anatomical projections of ascending sensory fibers. Brain regions not directly involved in either sensory or affective aspects of pain, such as the motor cortex, do not display microglial activation.[128] Hyperactivity in parts of the anterior cingulate cortex and other limbic structures drives the anxiety and depression that represent a co-morbidity of chronic and neuropathic pain.[7,129]

Blood-borne inflammatory mediators[130] from the site of peripheral injury increase the permeability of the blood–brain barrier.[33] This allows CNS neurons to access blood cells and the cytokines and chemokines they produce.[131] In addition, the selective activation of glia and immune cells in nociceptive pathways[125] likely reflects localized neurogenic neuroinflammation in response to enduring intense activity.[73]

Alterations in Descending Control of Spinal Processing

Spinal nociceptive processing is subject to modulation by descending serotonergic and noradrenergic pathways.[6,132] Descending inhibition is mediated via α_2-adrenoceptors and $5HT_7$ receptors whereas serotonergic activation of metabotropic $5HT_2$ receptors and ionotropic $5HT_3$ receptors facilitates transmission[7]. Brainstem excitatory pathways are more important in the maintenance than in the induction of pain and under these conditions, α2-noradrenergic inhibition is attenuated whilst facilitation through $5HT_2$ and $5HT_3$ receptors is enhanced.[7,132–134] Actions on these descending controls are thus likely to underlie the efficacy of tricyclic antidepressants and serotonin-noradrenaline reuptake inhibitors in pain management.[7,10]

Different Injuries and Different Etiologies

As already stated, different types of nerve injury provoke different types of behavioral or physiological response in both humans and animals.[1–4] Thus while mechanical allodynia produced in animals by SNI[13] persists for many weeks, that produced by CCI is short-lived and recovery is seen in about 4 weeks.[13,37] Similarly, changes in synaptic transmission in the superficial dorsal horn are more robust after sciatic CCI than after complete sciatic nerve section (axotomy).[92] These findings are consistent with the observation that CCI promotes stronger and more long-lasting upregulation of TNF-α, IL-1β, and CCL-2 than axotomy by nerve crush.[135] It has also been shown that the neuronal subtypes in the dorsal horn that are involved in generation of mechanical allodynia is defined by the nature of peripheral nerve injury.[136]

More clinically relevant observations include reports that neuropathic pain associated with multiple sclerosis is characterized by loss of spinal neurons[137] but this effect is not seen with CCI.[138,139] The above findings imply that different types of injury provoke the generation of different sets of mediators[18,140] and thus present different drug targets.

The Way Forward? Bridging the Gap between Basic Science and Clinical Practice

Given that patients with neuropathic pain are heterogeneous in pathophysiology, etiology, and clinical presentation[1,5] it is hardly surprising that injury-specific pathologies are found in animal models. As in the clinic, there is the added complication that signs of pain and response to medication of each experimental animal is determined by factors such as their sex, prior exposure to neonatal injury, age, intestinal microbiome, and environmental factors.[1–4,141,142]

Quantitative sensory testing (QST) may help to bridge the knowledge gap between clinical and laboratory findings. This involves formalization and quantification of a battery of neurological tests, such as response to von Frey filaments, vibration, heat, pressure, and cold as well as dynamic allodynia and wind-up ratio.[5] Findings are compared with datasets that represent normal responses to sensory tests. Neuropathic pain patients can then be grouped into clusters based on their sensory profiles and this may have a role in determining treatment.[143] Technological improvements in microneurography have shown that the specific C-fibre subpopulation affected (mechanoinsensitive versus non-mechanoceptive) depends on the source of neuropathic pain and the type of neuropathy.[144,145] Modern microneurography approaches will thus play a role in future refinement of QST. The validity of QST is supported by the observation that *post hoc* analysis of responders to treatments in clinical trials suggest that clinical effectiveness may cluster according to pain phenotype.[143] Beyond this, it may also be possible to subcategorize patients according to their cytokine profile. It then may be possible to correlate precisely quantified signs and symptoms in each individual patient to pathophysiology at the cellular and molecular level.

Recent improvements in basic science approaches also seek to bridge the gap between the "bench and bedside". For example, improved methodologies are starting to differentiate probable pain in animal models from nociception or simple withdrawal reflexes.[57,146] Also more attention is now paid to the genetics, environment, and sex of experimental animals[1,80] and improved methodologies are now available for bringing human tissue to the laboratory. These include the culture of human nociceptors either from surgical or post-mortem tissue or using human-induced pluripotent stem cell-derived nociceptors.[145,147]

Taken together, these approaches will permit a rational and highly personalized medicine approach that will dictate the most appropriate therapeutic approach for each individual patient.[7,148,149]

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