ОГЛЯДИ

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The Biology of Neuropathic Pain

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Nerve injury or disease often leads to intractable neuropathic pain. Axons which are severed undergo Wallerian degeneration. This involves the activation of Schwann cells, mast cells, fibroblasts, keratinocytes and epithelial cells and the release of inflammatory cytokines, chemokines and growth factors. These primary mediators sensitize sensory nerve endings, attract macrophages, neutrophils and lymphocytes, alter gene expression, promote post-translational modification of proteins and alter ion channel function. This evokes spontaneous activity in primary afferent neurons that is crucial for the onset and maintenance of pain. In addition, secondary mediators such as colony stimulating factor 1 are generated and released from primary afferent terminals. These promote release of tertiary mediators such as brain-derived neurotrophic factor and interleukin 1β from spinal microglia and astrocytes. Tertiary mediators facilitate the generation and transmission of nociceptive information by facilitating excitatory transmission and attenuating inhibitory transmission in the dorsal horn. Transfer of information between neurons and immune cells is bidirectional. Neurons directly control immune cell function in a process termed neurogenic neuroinflammation. Increased permeability of the blood-brain barrier allows access of immune cells to neurons in central pain pathways. This, together with neurogenic neuroinflammation, increases activity throughout the pain sensory system. This review provides an overview of processes involved in the generation and persistence of peripherally generated neuropathic pain. Attention is drawn to the idea that pain etiology is dependent on the nature of the injury and different processes operate in males compared to females.

Key words: neurogenic neuroinflammation; allodynia; dorsal horn; dorsal root ganglia; central sensitization; neuropathy; nerve injury; neuroimmunology; brain-derived neurotrophic factor.

INTRODUCTION

Neuropathic pain afflicts at least 7% of the world's population [1]. It is characterized by mechanical or cold-induced allodynia (touch or thermally-induced pain), hyperalgesia, bouts of spontaneous "electric shock like" pain and sometimes by a persistent burning pain known as causalgia [2]. It may be associated with co-morbidities such as anxiety and depression [3]. Unlike nociceptive pain, which warns an individual of actual or potential tissue injury, neuropathic pain is maladaptive and persists long after damaged tissue has healed and recovered [4]. It is frequently intractable and its high prevalence reflects its association with multiple disease states or injuries. These include trauma to peripheral nerve, spinal cord or brain as well as fibromyalgia, multiple sclerosis stroke, post herpetic neuralgia [2], migraine, osteoarthritis rheumatoid arthritis, autoimmune disease, complex regional pain syndromes, viral infections such as HIV and neuropathies associated with diabetes, chemotherapy and cancer itself [1].

Despite the association of neuropathic pain with so many clinical presentations, the available therapeutic approaches are limited. There is an urgent need to find new drugs and drug targets [2, 5, 6]. Most of the current understanding is derived from studies using peripheral nerve injury models in rodents. In most cases, the spared nerve injury (SNI) or chronic constriction injury (CCI) models are used [7]. This review focusses on generation of pain following peripheral nerve injury as overviewed by an

interrelated series of 8 complimentary steps that are enumerated in the following sections.

Injury-induced wallarian degeneration

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. These activated cells generate and release pro-inflammatory primary mediators such as tumor necrosis factor (TNF-α) [8] interleukins 1β, 15, 17 and 18 (IL-1β, IL-15, IL-17 and IL-18) [9], nerve growth factor (NGF) [10], monocyte chemoattractant protein 1 (MCP-1/CCL-2) [11], chemokine (C-X-C motif) ligands (CXCL-1) [12] and 12 (*CXCL-12*) [13], histamine, serotonin and substance P [14, 15] and the secreted glycoproteins Wnt3a (wingless-type mammary tumor virus integration site family member 3A) and Wnt5a [16] (Figure).

Structural remodeling of peripheral nerves

Spared nerve injury (SNI) [7] promotes degeneration of non-nociceptive low threshold afferents and their replacement by low threshold nociceptors. Mild tactile stimulation therefore produces mechanical allodynia [17]. In many cases, injury also provokes perivascular sympathetic fibres to sprout and to interact and excite sensory nerve terminals and DRG cell bodies [18].

Sensitization and spontaneous activity of primary afferents

The primary mediators described above sensitize peripheral nerve endings, axons and cell bodies of primary afferents. This is referred to as "peripheral sensitization". Mediators also promote plasma extravasation and increase the permeability of the blood brain barrier [19]. This and the chemoattractant properties of various mediators, facilitate the recruitment of immunocompetent leucocytes and lymphocytes to the site of injury [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. Satellite glial cells and macrophages in DRG [21] represent another source of inflammatory mediators. The actions of primary mediators culminate in marked changes in genes coding for neuropeptides, cytokines, chemokines, receptors, ion channels, signal transduction molecules and synaptic vesicle proteins. Some of these gene products also function as secondary

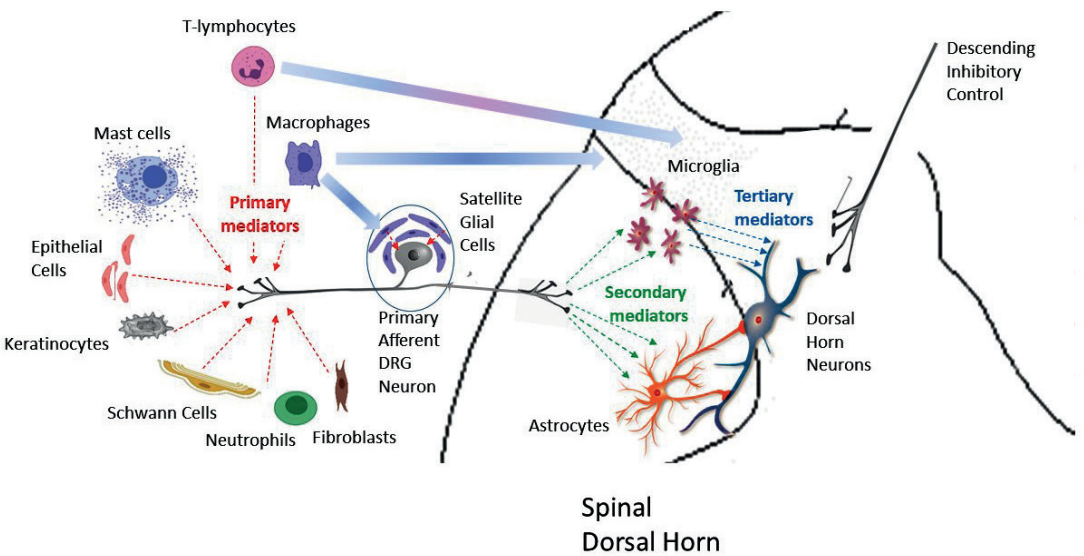

Diagram to show the actions of primary, secondary and tertiary mediators in the generation of pain following peripheral nerve injury

mediators (see below) that effect the transfer of information between damaged peripheral nerves and various cell types in the spinal dorsal horn [9]. Primary mediators also affect the expression of long non-coding RNA's [22] and microRNA's. The latter post-transcriptionally regulate the protein expression of hundreds of genes in a sequence-specific manner [23]. Transfer of microRNAs between cell types may be brought about the release and uptake of exosomes [24].

Altered function of ion channels as a result of the action of primary mediators leads to increased excitability of primary afferent neurons [25-28] and the generation of stimulus-independent spontaneous activity that is absolutely crucial for the onset and persistence of pain [29-31].

In particular, $Na_v1.7$, $K_v7.2$, $Ca_v2.2$, $Ca_v3.2$ and HCN2 channels have emerged as potential therapeutic targets for drug development [32-34]. As would be expected, the population of ion channels affected by primary mediators is similar to that affected by peripheral nerve injury [25, 26] and in animal models, blockade of the actions of primary mediators abrogates signs of injury-induced pain [4, 20, 35].

Bidirectional signalling between the nervous and immune systems and neurogenic neuroinflammation

Primary mediators derived from immune cells not only affect neurons, neuronal activity affects immune cells. This "neurogenic neuroinflammation" [36] is brought about by the release of neuropeptides and glutamate from primary afferents and their interaction with their cognate receptors on glia or immune cells [37].

Generation of secondary mediators. Transfer of information from the periphery to the spinal cord

As already mentioned, primary mediators not only increase primary afferent excitability they also promote the expression of secondary mediators. These are released into the spinal dorsal horn and include colony stimulating factor 1 (CSF-1), chemokine (C-C motif) ligand 21 (CCL-21), wingless-type mammary tumor virus integration site family, members 3A and 5A (Wnt3A, Wnt5a) and C-X-C motif chemokine 12 (CXCL-12) [9, 16, 38-41].

These secondary mediators influence the properties of both microglia and astrocytes in the dorsal horn. Spinal microglia are affected in male rodents [42] allowing them to detect and mount an enduring response to peripheral nerve injury. The chemokines CCL-21 and CXCL-12 signal to activate astrocytes [41].

Whereas microglia play a predominant role in males, invading macrophages and adaptive immune cells such as T-lymphocytes are involved in females [43, 44].

Glutamate from primary afferents can be regarded as a secondary messenger. In addition to producing synaptic potentials in neurons, it activates astrocytes, T-cells, endothelial cells and microglia by interaction with metabotropic glutamate receptors (mGluRs) [36].

Effects of secondary mediators in the dorsal horn and generation and release of tertiary mediators

The secondary mediators that are released from primary afferents activate their cognate receptors on spinal microglial cells and astrocytes (Figure). This leads to microglial and astrocyte activation and proliferation and the generation and release of tertiary mediators. In a similar fashion to nerve injury [45-47], brain derived neurotrophic factor (BDNF) facilitates excitatory synaptic transmission [48-51] and supresses inhibitory transmission in the spinal dorsal horn [6, 52] leading to spontaneous activity and the misprocessing of sensory information [53-56] (Figure). Blocking the action of BDNF using a function-blocking antibody against the TrkB receptor (anti-TrkB) or a BDNF-sequestering fusion protein (TrkB–Fc) reverse injury-induced allodynia in an animal model and intrathecal injection of recombinant BDNF provokes allodynia in naïve animals [52].

As already mentioned, in females, changes in sensory processing in the dorsal horn involve the

invasion of macrophages and T-lymphocytes [43, 44]. Yet as in males, this leads to attenuation of inhibition following collapse of the Cl^- gradient [57]. In females, collapse of the Cl^- gradient is also brought about by the neuropeptide, CGRP [58] which is released from primary afferent terminals.

Attenuation of inhibition [45, 56] and augmentation of excitation and long-term alteration of synaptic plasticity [6, 46, 54, 59-61], promote misprocessing of sensory information leading to "central sensitization" at both spinal and supra-spinal levels [62-65] .

This is associated with alterations in brain stem circuits that exert descending control of spinal circuitry [66] (Figure).

Changes in central sensory pathways and higher brain regions

Cytokine/chemokine/growth factor/glial cell interactions are also involved in modulation of sensory information in the mesolimbic system [67], thalamus, sensory cortex, nucleus accumbens and amygdala [68-70]. Peripheral nerve injury promotes microglial activation in the contralateral thalamus, sensory cortex and amygdala as would be expected from the anatomical arrangement of ascending sensory fibres. Brain regions not directly involved in either sensory or affective aspects of pain [3], such as the motor cortex, do not display microglial activation [68]. Blood borne inflammatory mediators [71] from the site of peripheral injury increase the permeability of the blood-brain barrier [19] and that of tight junctions between capillary endothelial cells. This allows CNS neurons to access blood cells and the cytokines and chemokines they produce [72]. In addition, the selective activation of glia and immune cells in nociceptive pathways [68] likely reflects localized neurogenic neuroinflammation in response to enduring intense activity [36].

Failure to resolve chronic neuroinflammation

All types of injury are associated with inflammation and pain and the interactions of inflammatory mediators such as IL-1β and TNF-α with neurons, glia, immunocompetent leucocytes and lymphocytes and macrophages [4]. Since identified "off signals" actively supress inflammation once the injured tissue has healed [73], the pain is usually acute. The signals that resolve inflammation and pain include anti-inflammatory cytokines such as IL-10 and lipid-derived specialized pro-resolving mediators (SPMs) [74] that are derived from omega-3 fatty acids. Neuroinflammation associated with neuropathic pain does not resolve, despite the physiological production and availability of SPM's and anti-inflammatory cytokines.

As already mentioned, spontaneous and ectopic activity in primary afferent fibres is crucial for the maintenance and persistence of signs of neuropathic pain [29-31]. Excessive neuronal activity releases glutamate and neuropeptides which interact with glia and immune cells to provoke the generation of inflammatory mediators [36]. It is possible that this incessant neurogenic neuroinflammation overcomes the resolution processes that normally terminate inflammation. This may contribute to the indefinite persistence of neuropathic pain.

In addition, the injury induced structural changes in peripheral afferent and sympathetic nerves [17, 18] are almost certainly irreversible. These enduring changes also contribute to the chronic nature of neuropathic pain.

Mediators of cellular interactions

As will be appreciated, a broad palate of inflammatory and neurotropic substances and their cognate receptors are involved as primary, secondary or tertiary mediators which promote the onset and maintenance of neuropathic pain [4, 9, 20, 35]. A brief description of some of the most important entities and their actions is of interest as they present as potential drug targets [6]. New therapeutic approaches are urgently required as those currently available are of limited effectiveness [2, 5, 6]. It should also be understood that identification of a selective ligand for a given receptor often fails to yield a therapeutically effective agent. This

transition may be compromised by unfavorable pharmacokinetics, toxicities and/or off target effects of the identified ligand.

Interleukin 1β (IL-1β)

IL-1β serves as both a primary and tertiary mediator [4, 9, 75]. Generation and processing of IL-1β depends on activation of caspase 1 [76] and the NLRP3 inflammasone [77]. It excites both DRG neurons [25-28] and neurons in the spinal dorsal horn [78, 79]. The action of IL-1β on primary afferent neurons contributes to the generation of ectopic activity that is critical to the onset and maintenance of pain [29-31]. IL-1β from microglia stimulates astrocytic production of both TNF–α and IL-1β itself [80] thereby amplifying the initial IL-1β signal.

Whereas its peripheral actions involve decreased K^+ channel activity and increased activity of Na^+ channels [25, 27] and T-type (Ca_v3) Ca^{2+}channels [81], spinal actions involve increases in excitatory synaptic transmission [78, 79]. 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) [82].

Despite the established role of IL-1β in neuropathic pain, the IL-1β antagonist anakinra is not listed amongst the first or second line treatments for neuropathic pain [5].

Other Interleukins

Whilst the evidence for a role for IL-15 and IL-17 in neuropathic pain is sparse, stronger evidence support the role of IL-18 as both a primary and tertiary messenger [83]. Thus nerve injury has been shown to upregulate both IL-18 in microglia and IL-18 receptor in astrocytes. Also, intrathecal injection of IL-18 induces behavioral, morphological, and biochemical changes similar to those observed after nerve injury and IL-18 blockade attenuates injury-induced tactile allodynia [84].

Tumour Necrosis Factor α (TNF-α)

TNF-α is also known as cachectin or cachexin. Its activation requires processing by metalloproteases [85]. Like IL-1β, TNF-α serves as both a primary [86] and tertiary mediator [87] and perhaps as a secondary mediator [88]. TNF-α augments excitatory transmission in the dorsal horn [78] as well as long term potentiation by an action on glial cells in a similar fashion to IL-1β [89]. Blockade of TNF-1 receptors attenuates neuropathic pain in male rodents but not in females [90]. Although anti-TNF antibodies and anti TNF drugs such as thalidomide are available, none seem particularly useful in pain management [91].

Chemokines

CCL-2 (also known as monocyte chemoattractant protein-1; MCP1) signals through the CCR-2 chemokine receptor. There is good evidence to suggest it functions as a primary messenger in pain generation [92]. Thus mice overexpressing CCL-2 show enhanced pain sensitivity and *ccr2* knock-out mice are resistant to the establishment of neuropathic pain [93]. DRG neurons are excited by CCL-2 [94] and transgenic mouse models have been used to directly visualize CCL-2 signaling via CCR-2 in DRG in the context of neuropathic pain [95]. CCL-2 is also expressed by microglia and invading macrophages [96]. Its presence in central structures may relate to its ability to alter the balance between excitation and inhibition in the nucleus accumbens [70].

CCL-21 (chemokine C-C motif ligand 21) produces pain-like behaviour in naive mice when administered by intrathecal injection. Impairment of CCL-21 function by blockade of its receptor (CXCR-3) diminishes nerve injury induced pain [97]. CCL-21 is upregulated in DRG following nerve injury, vesicles containing CCL-21 are preferentially transported into axons [98]. CCL-21 also affects microglial function [99] and it can be released from terminals of injured neurons [98]. Taken together, these findings suggest that CCL-21 may function as a secondary mediator between primary afferents and microglia following injury [9]. CCL-21 also signals to astrocytes [100].

CXCL-1 (chemokine C-X-C motif ligand 1) is upregulated in spinal astrocytes following peripheral nerve injury. Impairment of CXCL-1 function attenuates SNL-induced pain hypersensitivity whereas spinal application of CXCL1 augments it and promotes neuronal activation [101]. Its involvement in both peripheral and central sensitization has been reported [12].

CXCL-12 (chemokine C-X-C motif ligand 12). Peripheral nerve injury upregulates *CXCL-12 in DRG* [102] and its intrathecal administration induces hypersensitivity in naive rats [102]. In addition, CXCL-12 neutralizing antibodies or CXCL-12 antagonists transiently reverse allodynia after peripheral nerve injury or a model of diabetic neuropathy [103]. CXCL-12 thus serves a secondary messenger function by signalling from primary afferents to spinal astrocytes [41]. CXCL-12 also signals between astrocytes and microglia [102] and may be involved in hyperalgesic priming [104].

CX3CL-1 or Fractalkine. Nerve injury provokes *de novo* expression of fractalkine in dorsal horn astrocytes [105] and its upregulation in microglia and neurons. Intrathecal injection of fractalkine produces mechanical allodynia and thermal hyperalgesia whereas injection of a neutralizing antibody raised against its cognate receptor (CX3CR-1) delays the onset of mechanical allodynia and/or thermal hyperalgesia in neuropathic pain models [106]. Mice lacking CX3CR-1 do not display allodynia following peripheral nerve injury [107]. Nerve injury increases the level of soluble fractalkine in cerebrospinal fluid [108] and its release, which involves liberation of membrane bound fractalkine by cathepsin S appears obligatory for the expression of neuropathic pain [108]. Soluble fractalkine promotes microglia activation and the generation of tertiary mediators including IL-1β and TNF [106;109].

Since fractalkine immunoreactivity does not localize with markers of primary afferent terminals in the dorsal horn, it has been suggested that under neuropathic conditions, ongoing activity in primary afferent fibers induces release of cathepsin S from microglia [110] which liberates membrane bound fractalkine from dorsal horn neurons, thereby contributing to the amplification and maintenance of neuropathic pain [9, 108].

Despite attenuation of pain following inhibition of chemokine function in animal models, there are few reports of the development of chemokine antagonists or antibodies for therapeutic use.

Interferon gamma (IFN-γ)

IFN-γ induces both tactile allodynia and altered microglia function. Genetic ablation of the interferon receptor (IFN-gR) impairs nerve injury-evoked activation of ipsilateral microglia and tactile allodynia [111]. IFN-γ also increases dorsal horn excitability [112] and facilitates synaptic transmission between primary afferent C-fibres and Lamina 1 neurons via a microglial dependent mechanism [113]. Although the level of IFN-γ is increased in spinal cord following peripheral nerve injury [114] this may originate from invading T-lymphocytes. It may therefore play an important role in the microglia-independent pain seen in females [44].

Nerve Growth Factor (NGF)

Following nerve injury, NGF is involved in the long-term sensitization of peripheral nerves. This involves upregulation of CGRP and substance P in sensory neurons and increased sensitivity of nociceptors [10, 115]. Because it produces hyperalgesia when injected into human volunteers [115] and is secreted by activated macrophages [116], NGF serves as a primary mediator in the development of neuropathic pain. This is supported by the observation that anti-NGF suppresses pain in a variety of animal models, including spared nerve injury (SNI) [10]. There is considerable interest therefore in developing NGF antagonists as anti-allodynic agents. Unexpectedly however the anti-NGF monoclonal antibody tanezumab has been reported to produce hyperalgesia [117].

Colony Stimulating Factor 1 (CSF-1)

CSF-1 is also known as macrophage colony stimulating factor. Although it is perhaps the best characterised secondary mediator in the generation of chronic neuropathic pain [9, 38, 39, 118, 119] its actions are normally only seen in male rodents [43].

Injury-induced release of primary inflammatory mediators such as interleukin 1β from satellite glial cells and invading macrophages in DRG induce the *Csf1* gene in primary afferent neurons [21, 119-121]. mRNA for colony stimulating factor (CSF-1) and CSF-1 protein are also upregulated by nerve injury as is mRNA for the CSF-1 receptor in spinal microglia [38, 122, 123]. Intrathecal injection of recombinant CSF-1 induces microglial proliferation and renewal as well as mechanical allodynia in naïve male rodents but not in females [38, 39, 124-127]. When *Csf1* gene expression is selectively prevented in sensory neurons, nerve injury-induced CSF-1 expression and the development of mechanical hypersensitivity are prevented as is injury-induced microglial activation and proliferation [121].

A recent study showed that following injury, the spinal invasion of immunosuppressive regulatory T-lymphocytes attenuates the activation of microglia in females. This is supported by the observation that female mice engineered to lack regulatory T-lymphocytes show increased injury induced CSF1-induced microglial activation and pain hypersensitivity similar to that of males [127].

Release of CSF-1 from primary afferent terminals in males transforms the phenotype of resting microglia such that they expresses the ionotropic ATP receptor, P2X4 [38, 39, 118]. Taken together, with the observation that exposure of dorsal horn neurons to CSF-1 increases their excitability via a BDNF-dependent mechanism [118], these data strongly support its role as a secondary mediator signalling between injured primary afferents and microglia.

Brain Derived Neurotrophic Factor (BDNF)

The role microglial-derived BDNF as a tertiary messenger in central sensitization in male rodents is well established [9, 48, 50, 52, 59, 118, 128]. Intrathecal administration the BDNF binding protein TrkB-Fc prevents the development of mechanical allodynia after spared nerve injury (SNI) [129]. Also in males, release of the secondary mediator CSF-1 from injured primary afferents leads to the up regulation of BDNF in microglia [119]. ATP derived from dorsal horn neurons (and not primary afferents) [6, 130]) activates P2X4 receptors on microglia to promote Ca^{2+} influx and vesicular release of BDNF [131]. Wnt signalling can also promote BDNF release [132].

BDNF increases dorsal horn excitability by at least 4 mechanisms

First, it increases excitatory drive to excitatory dorsal horn neurons and inhibits that to inhibitory neurons by both presynaptic and postsynaptic mechanisms [49, 50, 118]. Although BDNF does not affect intrinsic excitability of dorsal horn neurons [50, 118], the altered synaptic activity is capable of increasing spontaneous action potential discharge in excitatory neurons whilst reducing it in inhibitory neurons [49]. This may be related to the observation that long-term exposure to BDNF inhibits spontaneous Ca^{2+} oscillations in some dorsal horn but unmasks it in others [59].

Secondly, BDNF enhances excitatory responses to NMDA in rat spinal cord *in vitro* [133]. This may involve potentiation of the function of presynaptic NMDA receptors on primary afferent terminals [134]. This further underlines the presynaptic effects of BDNF in the development of central sensitization.

Thirdly, peripheral nerve injury reduces expression of the potassium-chloride exporter (KCC2) in spinal lamina 1 neurons [45, 135] and pain projecting neurons in deep dorsal horn [136]. The resulting accumulation of intracellular Cl^- causes normally outward, inhibitory GABAergic synaptic currents mediated by Cl^- influx to become inward excitatory currents mediated by Cl^- efflux

[45]. It has also been shown that neurons in lamina I are more susceptible to changes in Cl^- gradient than those in lamina II [135] and biophysical and modelling analysis shows this loss is especially effective in promoting increased neuronal firing [137]. In male rats, BDNF mediates this downregulation of KCC2 [138]. Thus, administration of ATP activated microglia, but not control microglia, reproduces the shift in anion gradient seen after nerve injury as does application of BDNF. Also, blocking TrkB or using interfering RNA against BDNF reverses both injury induced pain behaviors and the shift in anion gradient [52]. Since loss of GABAergic inhibition enables non-noxious Aβ fiber-mediated excitatory transmission to acess the superficial spinal dorsal horn, this process plays an important role in the establishment of allodynia [55, 56, 139].

Fourthly, long term potentiation (LTP) of synaptic transmission contributes to central sensitization in the dorsal horn [140, 141]. LTP of C-fibre responses can also be augmented by BDNF [129] and LTP induced by high frequency nerve stimulation is occluded by BDNF pretreatment [142]. The importance of these effects was recently underlined by the observation that spinal LTP induced by high frequency stimulation as well as microglial activation and upregulation of BDNF are inhibited by antibodies to the tertiary mediator CSF-1. This strongly implicates microglial-derived BDNF in the generation of spinal LTP [143].

In addition to its actions on neurons, BDNF activates astrocytes which then release additional mediators that participate in the establishment of central sensitization [144, 145]. Astrocytes themselves are a source of BDNF [146], CSF-1 [23] LIF, IL-1β and TNF-α [147]. Astrocytic levels of each of these mediators is increased by injury.

MULTIPLICITY OF SIGNALLING PROCESSES

Different injuries and different mediators. Different types of nerve injury provoke different types of behavioral or physiological response in both humans and animals [148, 149]. Thus while mechanical allodynia produced by spared nerve injury (SNI) [7] persists for many weeks, that produced by chronic constriction injury (CCI) is short-lived and recovery is seen in about 4 weeks [7, 21]. Similarly, changes in synaptic transmission in the superficial dorsal horn are more robust after sciatic CCI than after axotomy by means of complete sciatic nerve section [47]. This result is consistent with the observation that CCI promotes stronger and more long lasting upregulation of TNF-α, IL-1β, and CCL-2 than nerve crush [150].

The above findings indicate that different types of injury provoke the generation of different sets of mediators and thus present different drug targets. Advances in the clinical treatment of pain may thus be realized by sub-classifying groups of patients according to the precise signs and symptoms they display [148].

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БІОЛОГІЯ НЕВРОПАТИЧНОГО БОЛЮ

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Пошкодження нервів або хвороби часто призводять до появи тяжкого невропатичного болю. Відповідні аксони зазнають так звані переродження Валеріана, що включає активацію шванівських клітин, мастоцитів, фібробластів, кератиноцитів , епітеліальних клітин та вивільнення цитокінів, хемокінів та факторів росту. Ці первинні медіатори сенсибілізують закінчення

сенсорних нервів, залучають макрофаги, нейтрофіли та лімфоцити, змінюють експресію генів, стимулюють посттрансляційну модифікацію білків та впливають на функцію іонних каналів, що призводить до генерації спонтанної активності у первинних аферентних нейронах та відповідно виникнення та підтримування болю. Крім того, утворюються та вивільняються з терміналів первинних аферентів вторинні медіатори, наприклад колоніє стимулюючий фактор 1. Це призводить до вивільнення з спинальної мікроглії та астроцитів третинних медіаторів, таких як мозковий нейротрофічний фактор та інтерлейкін 1β. Третинні медіатори полегшують збуджуючу та послаблюють гальмівну передачу у дорсальних рогах, що впливає на генерацію та передачу ноцицептивної інформації. Взаємодія нейронів та імунних клітин двобічна. Нейрони безпосередньо контролюють функції імунних клітин у процесі, який називається нейрогенне нейрозапалення. Підвищена проникність гематоенцефалічного бар'єра полегшує доступ імунних клітин до нейронів у центральних больових шляхах, що, разом з нейрогенним нейрозапаленням, призводить до зростання активності у больовій сенсорній системі в цілому. У цьому огляді розглянуто процеси, що відбуваються при виникненні та підтримуванні нейропатичного болю периферичного походження. Окрему увагу приділено залежності етіології болю від природи пошкодження та статевим відмінностям відповідних процесів.

Ключові слова: нейронне запалення; алодинія; дорсальний ріг; ганглії; центральна сенсибілізація; нейропатія; пошкодження нерва; нейроімунологія.

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