

Neuropathic Pain: Basic to Advanced Neuropathic Pain

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Abstract

As we know that pain is the most common reason for which a patient takes medicine. Pain is not a single entity but may be classified as nociceptive pain, inflammatory pain, and neuropathic pain. Nociceptive pain such pain can be healed or cured by using NSAIDs and other analgesics. Neuropathic pain is caused by the direct lesion on the neuron or damage or dysfunction of peripheral or central neurons. Minor neuropathic can cured automatically because peripheral nervous systems neuron surrounded by Schwann cell which promotes the healing of neurons but CNS neurons don't have Schwann cell they are covered with oligodendrocytes which don't have self healing property so pain mediated through CNS are generally chronic. Even the smallest stimulation results in spontaneous intense pain after that it gets transformed into chronic pain syndrome which is difficult to treat. In chronic pain syndrome, plastic changes occur in nociceptive neurons which cant be reversed by pharmacological treatment. In this review, we have discussed the core pathophysiology of neuropathic pain and advances in it to date.

Index terms— neuropathic, NSAIDs, oligodendrocytes, chronic.

1 Introduction

In Neuronal Signal Processing: Sequence process occurs between pain initiation and the pain experience through ascending pathway [1].

1. Transduction: It's the process by which a noxious signal gets transformed into an electrical signal so that it is carried towards the brain. In neuropathic, there is lesion or damage to the neurons so this mechanism is continuously on to produce the noxious signal. In the case of neuropathic pain when the nociceptor gets sensitized due to a signal it may recruit another silent receptor so that pain gets amplified this phenomenon is called Hyperalgesia. This afferent neuron sensitization is blocked by morphine by hyperpolarizing afferent neurons [2]. Neurons of this phase are termed as 1 st order neurons.

2 Transmission:

The phase in which noxious stimulus is carried or transmitted towards the spinal cord then to the thalamus and cortex. For transmission there two main primary afferent nociceptive neurons which conduct signal according to stimuli with different speed.

3 C-Fibers

? Nonmyelinated ? Signal conducting range 0.5-2m/sec Modulation: In this step, the noxious stimuli are modified intermediate neurons within the spinal cord and descending inhibitory system. Opioids act at the level of the spinal cord and inhibit dorsal horn neurons [3]. But beyond this morphine also produce its effect through periaqueductal central gray, medullary raphe, and spinal trigeminal nucleus too [4]. In the case of neuropathic pain descending inhibitory system is dysfunctional. ? Descending Modulatory system: This system activated at the level of periaqueductal (PAG) of the midbrain and these neurons then project downwards towards the medulla (nucleus reticularis gigantocellularis, nucleus raphe Magnus) and locus ceruleus which is the major source

7 ADVANCES IN NEUROPATHIC PAIN PATHOPHYSIOLOGY (RECEPTORS AND MEDIATORS)

42 of NE [5]. The name of the pathway is descending inhibitory pathway itself indicates that it will inhibit the
43 signal by promoting the release of neurotransmitters.

44 The distinct mechanism of Descending pain inhibitory pathways:

45 1. Descending neurons have direct contact with pain relay neurons of the spinal cord so electrical stimulation
46 of the brainstem causes hyperpolarization of nociceptive receptors in the spinal cord and the release of
47 neurotransmitters in descending pathway produces the inhibitory effect on ascending pathway so pain signal
48 gets blocked at the spinal level. 2. The central terminal of the primary afferent neuron lies in the spinal cord and
49 the central nociceptive receptor for neurotransmitter release in the spinal cord only by descending axon. To this
50 postsynaptic response evoked by dorsal root at lamina 2 reduced by NE. 3. Superficial laminae of the spinal cord
51 contain interneurons which contain inhibitory neurotransmitters like GABA, Glycine, Enkephalin. Descending
52 pathway excites these interneurons of the spinal dorsal horn this will inhibit the ascending pain signal.

53 Perception: From second-order neurons, the signal is handover to the 3rd order neurons. Third-order neurons
54 project to the somatosensory cortex and enable perception of pain through different parts [6]. Only Opioids able
55 to inhibit pain perception no other drug able to do this.

56 4 II.

57 5 Pathophysiology of Neuropathic Pain

58 Diseases which causes spinal cord lesion are spinal cord injury, syringomyelia, multiple sclerosis, transverse
59 myelitis, and neuromyelitis optica [7]. Peripheral neuropathies diabetes mellitus, HIV [8] and Leprosy,
60 chemotherapy, immune and inflammatory disorder. Because of peripheral nerve lesion, there is an alteration
61 in electrical properties of the sensory nerve which create the imbalance between the central excitatory and
62 inhibitory system leads to complexity and chronic neuropathic pain.

63 Peripheral Sensitization: This means the sensitization is limited to the periphery only or the sensitization in
64 which the brain and spinal cord are not involved.

65 Primary afferent neurons C-fibers and A-delta fibers are involved in peripheral sensitization these nociceptors
66 respond best to the noxious stimuli. These pathophysiological changes are accompanied by cellular and molecular
67 changes. The spontaneous activity of the injured nerve exactly matches with the expression of mRNA to increase
68 the population of voltage-gated sodium channels. This increase in the population of voltage-gated sodium channels
69 leads to the lowering of threshold potential. Now, this cluster of sodium channel not only accumulate at injured
70 nerve but also to the proximity of dorsal root ganglia [9]. So that's why pathophysiological changes in DRG are
71 of particular therapeutic interest because DRG doesn't have BBB so it's easily accessible for systemic therapies
72 [10]. Damage to peripheral nerve leads to upregulation of various receptor proteins which are expressed in very
73 less quantity in normal physiology [11]. Ex. Vanilloid receptor (TRPV1), TRPV4. There are shreds of evidence
74 that uninjured fibers also contribute to the pain signaling with injured fibers [12] Product Such as nerve growth
75 factor are released in the vicinity of the nerve fibers that might trigger the release of TNF alpha and expression
76 of the sodium channel, TRPV1, Adrenoreceptor thereby converts normal fibers into abnormal ones [13].III.

77 6 Central Sensitization

78 Sensitization in the spinal cord-As a consequence of peripheral sensitization secondary changes occurs in the
79 spinal cord dorsal horn. Peripheral neuronal damage leads to an increase in excitability of wide dynamic range
80 neurons(WDRN). Wide dynamic range neurons are the neurons that respond to both painful and non-painful
81 stimuli [14]. These neurons behave or work in graded response means as the strength of noxious stimulus
82 increases results in increased pain sensation. This leads to hyperexcitability called central sensitization. This
83 sensitization is maintained by pathological C-fibers by sensitizing the spinal cord dorsal horn to release glutamate
84 act on postsynaptic NMDA receptor and neuropeptide substance P [15]. Central sensitization is maintained by
85 an intracellular cascade of mitogenactivated protein kinase(MAPK) [16]. As soon as central sensitization is
86 established then a small stimulus will responsible for the activation pain signal through low threshold A-beta
87 and A-delta mechanoreceptor [17]. Central N-type of calcium channel located presynaptic membrane of primary
88 afferent neuron plays important role in central sensitization by facilitating glutamate and substance P release
89 [18].

90 7 Advances in Neuropathic Pain Pathophysiology (Receptors 91 and Mediators)

92 ? Toll-like receptor 7

93 Toll-like receptor 7 contributes to neuropathic pain by activating NF- κ B in primary sensory neurons. Toll-
94 like receptors (TLRs) are a family of transmembrane pattern recognition receptors that mediate innate and
95 adaptive immunity by recognizing exogenous ligands, pathogen-associated molecular patterns(PAMP), and
96 danger-associated molecular patterns(DAMPs) [19]. TLRs not only expressed by the immune system but also
97 neurons and nonneuronal cells express this receptor. To explore the potential role of DRG TLR7 in neuropathic
98 pain, they examined whether TLR7 expression was altered in DRG and spinal cord following unilateral L4 A
99 SNL, and results revealed that SNL, but not sham surgery, led to the time-dependent increases in expression of

100 Tlr7 mRNA and its protein in the ipsilateral L4 (injured) DRG on days 3, 7, and 14 post-SNL. So they have
101 further studied blocking of these TLR7 attenuates the pain hypersensitivity. so this overall result shows that
102 DRG overexpression of TLR7 leads to neuropathic pain symptoms [20]. Increased expression of TLR7 increases
103 the activation of NF- κ B in injured DRG leads to neuropathic pain symptoms.

104 ? TLR8 in the Trigeminal Neuropathic Pain in Mice TLR8 is located in the intracellular endoplasmic reticulum
105 (ER), endosomes, and lysosomes of DRG neurons, and plays an important role in the pathogenesis of spinal nerve
106 injury-induced neuropathic pain [21]. TLR8 is mainly expressed in DRG and its expression is upregulated after
107 SNL. Concluding pieces of evidence shown that TLR8 is necessary for maintaining neuropathic pain. This is
108 achieved by delivering siRNA which will exclusively attenuate the TLR8 mediated pain state like mechanical
109 allodynia and hyperalgesia. The results have been shown that TLR8 Expression is Increased in TG Neurons
110 After pIONL-Induced TNP. Deletion of Tlr8 Reduces the pIONL-Induced Activation of ERK and p38, and the
111 Expression of Pro-inflammatory Cytokines in the TG. Intra-TG Injection of TLR8 Agonist VTX-2337 Induces
112 Pain Hypersensitivity. TLR8 Agonist VTX-2337 Increases the Ca²⁺ Concentration in TG Neurons [22].

113 ? TLR signaling adaptor protein MyD88 in neuropathic pain.

114 The myeloid differentiation factor-88 adaptor protein (MyD88) mediates most TLRs (except for TLR3)
115 signaling, as well as Toll/Interleukin receptor domain signaling through the interleukin (IL)-1 and IL-18 receptors.
116 This protein in primary sensory neurons contributes to persistent inflammatory and neuropathic pain along with
117 neuroinflammation. Studies have shown that selective deletion of Myd88 in Na v 1.8-expressing primary sensory
118 neurons in CKO mice leads to reductions incomplete Freund's adjuvant (CFA) induced inflammatory and chronic
119 constriction injury (CCI) induced neuropathic pain in the maintenance phase, without affecting basal pain and
120 acute inflammatory pain [23].

121 ? Sphingosine-1 phosphate receptor-1 in neuropathic pain S1PR1 Activation in astrocytes contributes to
122 neuropathic pain. Based on genetic and pharmacological inhibition of S1PR1 with the different antagonists from
123 different classes attenuated or even reversed neuropathic pain. S1PR1 Antagonist retains their capability to
124 inhibit neuropathic pain without affecting endogenous circuitry. However, this is limited to astrocyte-specific
125 activation of S1PR1 [24]. In addition to this administration of selective S1PR1 agonist SEW2871 [25] caused the
126 development of mechanohypersensitivity in naïve mice [26]. S1P antagonism by FTY720/fingolimod results in a
127 decreased chemotherapy-induced neuropathic pain [27]. Fingolimod also able to reduce the neuropathic pain in
128 MS by inhibiting S1PR1 dependent central sensitization of the dorsal horn [28].

129 8 ? P2X4 receptor in neuropathic pain

130 ? PARP-1-Regulated TNF-Alpha expression in Neuropathic pain Poly-(ADP-Ribose) Polymerase 1 a Transcription
131 regulator for TNF-Alpha. Its expression in DRG and SDH(Spinal Dorsal Horn) contributes to neuropathic
132 pain pathogenesis in rats. This has the basis of lumbar 5 nerve ligation (L5 SNL) resulted in increased expression
133 and activation of PARP-1 in DRG and the spinal dorsal horn [34]. PARP-1 Inhibitors impaired neuropathic
134 pain states indicate their role in neuropathic pain. Studies have shown that PARP-1 involved in the regulation
135 of inflammatory processes and functionally associated with transcription factor NF-Kappa B contributes to
136 chronic inflammatory diseases [35]. A new concept of evoking neuropathic pain was proposed in which spinal
137 microglia are activated after PNI(Peripheral Nerve Injury), and P2X4Rs on these activated microglia have an
138 important role in evoking neuropathic pain [29]. P2X4 Receptor role in neuropathic pain is well established. The
139 SNRIs duloxetine has an inhibitory effect on the function of microglial P2X4R so it's used in neuropathic pain
140 treatment. Duloxetine inhibited microglial P2X4R function in addition to that Intrathecal administration of
141 duloxetine attenuates mechanical allodynia after PNI(Peripheral Nerve Injury) that may be because of possible
142 involvement of P2X4R [30]. Upregulation of this ion gated receptor P2X4Rs is might be connected to fibronectin/
143 integrin-dependent mechanism based on finding made on echistatin which blocks beta1 and beta3 integrins.
144 In vitro studies have shown that echistatin down regulates the P2X4Rs upregulation [31]. P2X receptors are
145 nonselective cation channels that open in response to ATP binding, allowing the rapid flow of ions (K⁺, Na⁺
146 , Ca²⁺) across the membrane but the calcium permeability is highest in the case of P2X4Rs, and stimulation
147 of these receptors leads to the activation of p38 MAPK. This results in p38 MAPK activation and BDNF release
148 as a key step in microglia-neuron communication leading to nerve injury-induced pain hypersensitivity [32]. This
149 signaling further activates PLA 2 liberating arachidonic acid (AA) and release of prostaglandin E2 (PGE 2) that
150 leads to hypersensitivity of peripheral pain pathways [33].

151 ? CCL2 (monocyte chemoattractant protein-1, MCP-1) in Neuropathic Pain Activation of spinal microglia
152 plays a critical role in neuropathic pain. Studies have shown that intrathecal CCL2 leads to spinal microglial
153 activation and a neuropathic pain-like state. This acts as a precursor for understanding the further role of CCL2.
154 Neutralizing Antibodies against CCL2 lead to inhibition of neuropathic pain behavior and microglial activation
155 [36]. Thus CCL2 is involved in immune activation and maintaining sensitivity in neuropathic pain. Ryk (receptor-
156 like tyrosine kinase) mediates excitatory synaptic transmission and also releases CCL2 in neuropathic pain and
157 antagonism of RyK leads to decreased CCL2 [37]. So because of this role modulation or inhibition of CCL2
158 responsible for attenuation of neuropathic pain. Minocycline is under study for neuropathic pain and its already
159 been proven that it acts through down regulating microglial activation CCL2 and CCR2 [38].

160 ? Melanocortin Type-4 Receptor in Neuropathic Pain Melanocortin type-4 receptor is stimulated after nerve
161 injury by α -MSH (Melanocortin Stimulating Hormone). This result in tonic pronociceptive response leads to

162 sustaining the neuropathic pain. This idea leads to the development of a bifunctional compound which will act as
163 an agonist on opioid receptor and antagonist of MC4 (Melanocortin 4 Receptor). Such compound produced effect
164 at very low dose without affecting motor coordination in CCI mice [39]. It also investigated that MC4 Antagonism
165 produced analgesia, anti-allodynic, anti-nociception and this observation further strengthen by Ligands VVK052
166 and VVK054 which show excellent affinity towards the human MC4 Receptor [40]. Tolerance in the case of
167 opioid therapy is obvious the use of bifunctional ligand also shown the capability to decrease the tolerance
168 [41]. These results showed the possibility of the melanocortin system and its receptor in neuropathic pain.
169 Withdrawal symptoms and ?-MSH induced hyperalgesia attenuated by the melanocortin-4 Receptor antagonist.
170 The widespread distribution of melanocortin might be widely associated with neuropathic pain [42]. So prolonged
171 blockade of melanocortin receptor (most probably MC4) results in alleviation or decreased of allodynia in rats
with neuropathic pain [43].^{1 2}

A-delta fibers

? Thin

? Myelinated

? Signal conducting range 2-20m/sec

? Generally, respond to only high threshold
mechanical stimulation because to open such fibers
strong stimulus is required to initiate and transmit
the noxious signal. Because they require high
potential to activate called High Threshold
Mechanoreceptors.

? Some delta fibers respond to thermal stimuli also
termed Mechano-thermal receptor.

? Neurons of this phase are termed second-order
neurons and sensitization of these neurons called
central sensitization leads to hyperalgesia and
allodynia later.

Figure 1:

172

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