Global Journal of Medical Research: a
Neurology & Nervous System
Volume 21 Issue 3 Version 1.0 Year 2021
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Neuropathic Pain: Basic to Advanced Neuropathic Pain

By Santosh Nagare
Banaras Hindu University

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 Schwan 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.

Keywords: *neuropathic, NSAIDs, oligodendrocytes, chronic.*

GJMR-A Classification: *NLMC Code: WL 103.5*

Strictly as per the compliance and regulations of:

Neuropathic Pain: Basic to Advanced Neuropathic Pain

Santosh Nagare

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 Schwan 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.

Keywords: neuropathic, NSAIDs, oligodendrocytes, chronic.

I. Introduction

Steps 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 1st order neurons.
2. Transmission: The phase ion 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.

C- Fibers

- Nonmyelinated
- Signal conducting range 0.5-2m/sec
- Sensitive to mechanical, thermal, chemical stimuli hence called C-polymodal nociceptors.

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.

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

Corresponding Author: (M.Pharm), Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, Uttar Pradesh, India.
e-mail: santoshnagare11061997@gmail.com

The distinct mechanism of Descending pain inhibitory pathways:

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

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

II. Pathophysiology of Neuropathic Pain

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

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

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

III. Central Sensitization

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

Advances in Neuropathic Pain Pathophysiology (Receptors and Mediators)

- Toll-like receptor 7

Toll-like receptor 7 contributes to neuropathic pain by activating NF-κ Binprimary sensory neurons. Toll-like receptors (TLRs) are a family of transmembrane pattern recognition receptors that mediate innate and adaptive immunity by recognizing exogenous ligands, pathogen-associated molecular patterns(PAMP), and danger-associated molecular patterns(DAMPs)[19]. TLRs not only expressed by the immune system but also neurons and nonneuronal cells express this receptor. To explore the potential role of DRG TLR7 in neuropathic pain, they examined whether TLR7 expression was altered in DRG and spinal cord following unilateral L4

SNL, and results revealed that SNL, but not sham surgery, led to the time-dependent increases in expression of Tlr7 mRNA and its protein in the ipsilateral L4 (injured) DRG on days 3, 7, and 14 post-SNL. So they have further studied blocking of these TLR7 attenuates the pain hypersensitivity. so this overall result shows that DRG overexpression of TLR7 leads to neuropathic pain symptoms[20]. Increased expression of TLR7 increases the activation of NF-Kb in injured DRG leads to neuropathic pain symptoms.

- TLR8 in the Trigeminal Neuropathic Pain in Mice

TLR8 is located in the intracellular endoplasmic reticulum (ER), endosomes, and lysosomes of DRG neurons, and plays an important role in the pathogenesis of spinal nerve injury-induced neuropathic pain[21].TLR8 is mainly expressed in DRG and its expression is upregulated after SNL. Concluding pieces of evidence shown that TLR8 is necessary for maintaining neuropathic pain. This is achieved by delivering siRNA which will exclusively attenuate the TLR8 mediated pain state like mechanical allodynia and hyperalgesia. The results have been shown that TLR8 Expression is Increased in TG Neurons After pIONL-Induced TNP. Deletion of *Tlr8* Reduces the pIONL-Induced Activation of ERK and p38, and the Expression of Pro-inflammatory Cytokines in the TG. Intra-TG Injection of TLR8 Agonist VTX-2337 Induces Pain Hypersensitivity. TLR8 Agonist VTX-2337 Increases the Ca^{2+} Concentration in TG Neurons[22].

- TLR signaling adaptor protein MyD88 in neuropathic pain.

The myeloid differentiation factor-88 adaptor protein (MyD88) mediates most TLRs (except for TLR3) signaling, as well as Toll/Interleukin receptor domain signaling through the interleukin (IL)-1 and IL-18 receptors. This protein in primary sensory neurons contributes to persistent inflammatory and neuropathic pain along with neuroinflammation. Studies have shown that selective deletion of *Myd88* in $Na_v1.8$-expressing primary sensory neurons in CKO mice leads to reductions incomplete Freund's adjuvant (CFA) induced inflammatory and chronic constriction injury (CCI) induced neuropathic pain in the maintenance phase, without affecting basal painand acute inflammatory pain[23].

- Sphingosine-1 phosphate receptor- 1 in neuropathic pain

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

- P2X4 receptor in neuropathic pain

A new concept of evoking neuropathic pain was proposed in which spinal microglia are activated after PNI(Peripheral Nerve Injury), and P2X4Rs on these activated microglia have an important role in evoking neuropathic pain[29]. P2X4 Receptor role in neuropathic pain is well established. The SNRIs duloxetine has an inhibitory effect on the function of microglial P2X4R so it's used in neuropathic pain treatment. Duloxetine inhibited microglial P2X4R function in addition to that Intrathecal administration of duloxetine attenuates mechanical allodynia after PNI(Peripheral Nerve Injury) that may be because of possible involvement ofP2X4R[30]. Upregulation of this ion gated receptor P2X4Rs is might be connected to fibronectin/ integrin-dependent mechanism based on finding made on echistatin which blocks beta1 and beta3 integrins. In vitro studies have shown that echistatin down regulates the P2X4Rs upregulation[31]. P2X receptors are non-selective cation channels that open in response to ATP binding, allowing the rapid flow of ions (K^+, Na^+, Ca^{2+}) across the membrane but the calcium permeability is highest in the case of P2X4Rs, and stimulation of these receptors leads to the activation of p38 MAPK. This results in p38 MAPK activation and BDNF release as a key step in microglia-neuron communication leading to nerve injury-induced pain hypersensitivity[32]. This signaling further activates PLA_2 liberating arachidonic acid (AA) and release of prostaglandin E2 (PGE_2) that leads to hypersensitivity of peripheral pain pathways[33].

- PARP-1- Regulated TNF-Alpha expression in Neuropathic pain

Poly-(ADP-Ribose) Polymerase 1 a Transcription regulator for TNF-Alpha. Its expression in DRG and SDH(Spinal Dorsal Horn) contributes to neuropathic pain pathogenesis in rats. This has the basis of lumbar 5 nerve ligation (L5 SNL) resulted in increased expression and activation of PARP-1 in DRG and the spinal dorsal horn[34]. PARP-1 Inhibitors impaired neuropathic pain states indicate their role in neuropathic pain. Studies have shown that PARP-1 involved in the regulation of inflammatory processes and functionally associated with transcription factor NF-Kappa B contributes to chronic inflammatory diseases[35].

- CCL2 (monocyte chemoattractant protein-1, MCP-1) in Neuropathic Pain

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

- Melanocortin Type-4 Receptor in Neuropathic Pain

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

References Références Referencias

1. Vanderah, T.W.J.M.C., Pathophysiology of pain. 2007. 91(1): p. 1-12.
2. Yam, M.F., et al., General pathways of pain sensation and the major neurotransmitters involved in pain regulation. 2018. 19(8): p. 2164.
3. Basbaum, A., C. Clanton, and H.J.P.o.t.N.A.o.S. Fields, Opiate and stimulus-produced analgesia: functional anatomy of a medullospinal pathway. 1976. 73(12): p. 4685-4688.
4. Hökfelt, T., et al., Immunohistochemical analysis of peptide pathways possibly related to pain and analgesia: enkephalin and substance P. 1977. 74(7): p. 3081-3085.
5. de Leon-Casasola, O.A.J.A.N.C., Pain pathways, and mechanisms of neuropathic pain. 2007. 23(3).
6. Rajneesh, K. and R. Bolash, Pathways of pain perception and modulation, in Fundamentals of Pain Medicine. 2018, Springer. p. 7-11.
7. Watson, J.C., and P. Sandroni. Central neuropathic pain syndromes. in Mayo clinic proceedings. 2016. Elsevier.
8. Stavros, K. and D.M.J.C.H.A.R. Simpson, Understanding the etiology and management of HIV-associated peripheral neuropathy. 2014. 11(3): p. 195-201.
9. Baron, R.J.N.c.p.N., Mechanisms of disease: neuropathic pain—a clinical perspective. 2006. 2(2): p. 95-106.
10. Jacobs, J.M., R.M. Macfarlane, and J.J.J.o.t.n.s. Cavanagh, Vascular leakage in the dorsal root ganglia of the rat, studied with horseradish peroxidase. 1976. 29(1): p. 95-107.
11. Caterina, M.J., et al., Impaired nociception and pain sensation in mice lacking the capsaicin receptor. 2000. 288(5464): p. 306-313.
12. Wasner, G., et al., Postherpetic neuralgia: Topical lidocaine is effective in nociceptor–deprived skin. 2005. 252(6): p. 677-686.
13. Hudson, L., et al., VR1 protein expression increases in undamaged DRG neurons after partial nerve injury. 2001. 13(11): p. 2105-2114.
14. Kelly, D.J., M. Ahmad, and S.J.J.C.j.o.a. Brull, Preemptive analgesia I: physiological pathways and pharmacological modalities. 2001. 48 (10): p. 1000-1010.
15. Bennett, G.J.J.J.o.p. and s. management, Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. 2000. 19(1): p. 2-6.
16. Ji, R.-R. and C.J.J.N.o.d. Woolf, Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. 2001. 8(1): p. 1-10.
17. Tal, M. and G.J.J.P. Bennett, Extra-territorial pain in rats with a peripheral mononeuropathy: mechano-hyperalgesia and mechano-allodynia in the territory of an uninjured nerve. 1994. 57(3): p. 375-382.
18. Luo, Z.D., et al., Upregulation of dorsal root ganglion α2δ calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. 2001. 21(6): p. 1868-1875.
19. Akira, S., S. Uematsu, and O.J.C. Takeuchi, Pathogen recognition and innate immunity. 2006. 124(4): p. 783-801.

20. He, L., et al., Toll-like receptor 7 contributes to neuropathic pain by activating NF-κB in primary sensory neurons. 2020. 87: p. 840-851.
21. Zhang, Z.-J., et al., TLR8 and its endogenous ligand miR-21 contribute to neuropathic pain in murine DRG. 2018. 215(12): p. 3019-3037.
22. Zhao, L.-X., et al., TLR8 in the Trigeminal Ganglion Contributes to the Maintenance of Trigeminal Neuropathic Pain in Mice. 2020: p. 1-13.
23. Liu, X.-J., et al., TLR signaling adaptor protein MyD88 in primary sensory neurons contributes to persistent inflammatory and neuropathic pain and neuroinflammation. 2016. 6(1): p. 1-11.
24. Chen, Z., et al., Sphingosine-1-phosphate receptor 1 activation in astrocytes contributes to neuropathic pain. 2019. 116(21): p. 10557-10562.
25. Sanna, M.G., et al., Sphingosine 1-phosphate (S1P) receptor subtypes S1P1 and S1P3, respectively, regulate lymphocyte recirculation and heart rate. 2004. 279(14): p. 13839-13848.
26. Janes, K., et al., The development and maintenance of paclitaxel-induced neuropathic pain require activation of the sphingosine 1-phosphate receptor subtype 1. 2014. 289(30): p. 21082-21097.
27. Singh, S.K. and S.J.A.i.b.r. Spiegel, Sphingosine-1-phosphate signaling: a novel target for simultaneous adjuvant treatment of triple-negative breast cancer and chemotherapy-induced neuropathic pain. 2020. 75: p. 100670.
28. Doolen, S., et al., Fingolimod reduces neuropathic pain behaviors in a mouse model of multiple sclerosis by a sphingosine-1 phosphate receptor 1-dependent inhibition of central sensitization in the dorsal horn. 2018. 159(2): p. 224.
29. Tsuda, M., et al., P2X 4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. 2003. 424(6950): p. 778-783.
30. Yamashita, T., et al., Duloxetine inhibits microglial P2X4 receptor function and alleviates neuropathic pain after peripheral nerve injury. 2016. 11(10): p. e0165189.
31. Tsuda, M., et al., Fibronectin/integrin system is involved in P2X4 receptor upregulation in the spinal cord and neuropathic pain after nerve injury. 2008. 56(5): p. 579-585.
32. Stokes, L., et al., P2X4 receptor function in the nervous system and current breakthroughs in pharmacology. 2017. 8: p. 291.
33. Basbaum, A.I., et al., Cellular and molecular mechanisms of pain. 2009. 139(2): p. 267-284.
34. Gao, Y., et al., PARP-1-regulated TNF-α expression in the dorsal root ganglia and spinal dorsal horn contributes to the pathogenesis of neuropathic pain in rats. 2020. 88: p. 482-496.
35. García, S. and C.J.M.o.i. Conde, The role of poly (ADP-ribose) polymerase-1 in rheumatoid arthritis. 2015. 2015.
36. Thacker, M.A., et al., CCL2 is a key mediator of microglia activation in neuropathic pain states. 2009. 13(3): p. 263-272.
37. Yang, Q.O., et al., Ryk receptors on unmyelinated nerve fibers mediate excitatory synaptic transmission and CCL2 release during neuropathic pain induced by peripheral nerve injury. 2017. 13: p. 1744806917709372.
38. Piotrowska, A., et al., Direct and indirect pharmacological modulation of CCL2/CCR2 pathway results in attenuation of neuropathic pain—in vivo and in vitro evidence. 2016. 297: p. 9-19.
39. Starnowska-Sokół, J., et al., Novel hybrid compounds, opioid agonist+ melanocortin 4 receptor antagonist, as efficient analgesics in mouse chronic constriction injury model of neuropathic pain. 2020. 178: p. 108232.
40. Kulkarni, V.V., et al., Novel analogs of bifunctional ligands for opioid and melanocortin 4 receptor, in Peptides for Youth. 2009, Springer. p. 195-196.
41. Piotrowska, A., et al., Novel bifunctional hybrid compounds designed to enhance the effects of opioids and antagonize the pronociceptive effects of nonopioid peptides as potent analgesics in a rat model of neuropathic pain. 2021. 162(2): p. 432.
42. Vrinten, D.H., et al., Neuropathic pain: a possible role for the melanocortin system? 2001. 429(1-3): p. 61-69.
43. Vrinten, D.H., et al., Chronic blockade of melanocortin receptors alleviates allodynia in rats with neuropathic pain. 2001. 93(6): p. 1572-1577.