Review Article

Mechanisms of Neuropathic Pain

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Abstract

Neuropathic pain has been concerning medical practitioners for quite some time. It is very common and occurs in almost 1% of world population. It is characterised by a pain sensation for a prolonged period with or without any stimulation. It may be caused due to any genetic anomaly or due to severe injury to the nervous system. The exact mechanism behind its occurrence is not known though studies show various changes at peripheral and central nervous system level that may lead to neuropathic pain. Various changes at tissue, cell and genetic level have been associated with neuropathic pain. This article aims at compiling recent findings related to the mechanisms of development of neuropathic pain at a molecular, CNS and PNS level.

Key words: Idiopathic, Mechanism, Neuropathic pain, Neuropathy, Nervous

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Introduction

Neuropathic pain is defined by the IASP (International Association for Study of Pain) as "*pain initiated or caused by a primary lesion or dysfunction of the nervous system*" (Vranken, 2009). Neuropathic pain often occurs after damage to the peripheral nervous system (PNS) or central nervous system (CNS) and its symptoms include spontaneous pain, augmented pain from noxious stimulation (hyperalgesia) and pain induced by normally non-noxious stimulation (allodynia) (Jeon and Youn, 2015). There is often sensation of a continuous pain and electric shock. These pain sensations lead to a disruption in daily routine and cause loss of ability to work. It may be present both in presence or absence of a stimulus. Pain syndromes may be divided into two groups-central and peripheral. Peripheral neuropathic pain includes diabetic peripheral neuropathic pain, HIV-associated neuropathy, plexopathy following trauma etc. Examples of

central neuropathic pain includes post stroke pain, syringomyelia, post ischemic myelopathy, pain associated with Parkinson's disease or multiples sclerosis etc. (Vranken, 2009). The mechanism of neuropathic pain is still unclear in spite of extensive investigations. Several experimental models of peripheral mononeuropathy in rats were developed wherein chronic constriction injury (Bennett and Xie, 1998) or partial lesion (Seltzer, 1990) of sciatic nerve or its root (Lutz, 2014) was done.

Molecular Processes in Neuropathic Pain

Various epigenetic mechanisms have been known to suppress/enhance gene expressions without altering the primary DNA sequence (Descalzi and Daigo, 2015). These mechanisms have been proved to be involved in synaptic plasticity which is a direct cause of neuropathic pain. These include miRNA (micro RNA) expressions that regulate neuropathic pain. miRNA is a class of non-coding inhibitory RNA that play an important role in regulating pain-processing within a wide range of experimental pain disorders (Kim and Chung, 1992; Millan, 1999). It is a new class of ssRNA of 19-24 nucleotides that modulate a large part of genome post-transcriptionally (Bartel, 2009). They bind to 3' UTR or sometimes 5' UTR of multiple RNA targets to which they are variably complementary. This allows a single miRNA to inhibit multiple genes (Thomson *et al.,* 2011). Various types of miRNA increase or decrease in different quantities based on site of stimulation for neuropathic pain e.g.- increase in miRNA after Spinal cord injury(SCI)- miR-21, miR-221, miR-223, miR-341, and decrease in miRNA after SCI- miR-124, miR-137, miR-181a, miR-219-2-3p, miR-7a (Andersen *et al.,* 2014).

Recently histone acetylation caused by Histone Acetyl Transferases (HATs) has been related to neuropathic pain a prominent change in the dorsal horn of spinal cord after SCI is the upregulation of HDAC1 (Histone Deacetylase 1) and the reduction of histone H3 acetylation (Cherng, 2013). The administration of HDAC inhibitors like baicalin and valproic acid alleviate SPL induced hyperalgesia and allodynia. It is also believed that NO along with peroxynitrites i.e. product of its reaction with superoxide radicals is involved in mechanism responsible for hyperalgesia in chronic pain. Increased production of NO locally has been shown to be important in maintenance of pain in neuropathic rats which is alleviated by NO synthase inhibitors. The hyperalgesia is increased by NO precursor L-arginine and NO donors sodium nitroprusside and S-nitroso-N-acetylpenicillamine (Naik *et al.,* 2006).

Peripheral Processes in Neuropathic Pain

After direct nerve damage, a local inflammatory response occurs. Around the site of injury nociceptive primary afferent neurons (PAF), damaged tissue, infiltration of inflammatory cells, vasculature, and sympathetic terminals result in the release of an inflammatory "soup". This "soup" includes histamine, bradykinin, serotonin, adenosine triphosphate, products from the cyclooxygenase (prostaglandin E2) and

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lipoxygenase pathways (leukotriene B4) of arachidon acid metabolism, protons, nerve growth factor (NGF), and cytokines (IL-1, IL-6, TNF). There is proof that NO is an important mediator of hyperalgesia in the central nervous system. In addition, degenerating nociceptive neurons release both Calcitonin-Gene Related Peptide (CGRP) and Substance P (SP). These neuropeptides trigger vasodilatation and extravasations and regulate secretion of inflammatory mediators from mast cells and leukocytes (neurogenic inflammation). Because of this inflammation, nociceptors, which are rather inactive and unresponsive to stimuli in normal circumstances, may show enhanced sensitivity with development of spontaneous discharges (Kynast, 2013; Sommer and Kress, 2004).

Upon PAF injury, the density and function of ion channels change, causing abnormal electric impulses and afferent input to the dorsal horn. N-type-voltage sensitive Ca2+-channels (VSCC), which play an important role in neurotransmission, become overactive and cause ectopic firing of these nerve endings (spontaneously and in response to stimulation) and neuronal hyper excitability (Altier and Zamponi, 2004; Dickenson, 2002). Non-synaptic interactions between neurons occur in the dorsal root ganglia and increase the already existing neuronal hyper excitability causing mechanical allodynia by interaction of C-fibers and Aβ-fibers. Aβ-fibers express SP and CGRP (normally expressed by C-fibers and Aδ-fibers), a phenotypic switch that may contribute to abnormal, pronociceptive actions following stimulation. Thus, Aβ-fibers, activated by low threshold, mechanical stimuli may release SP, CGRP, and brain-derived neurotrophic factor (BDNF) in the dorsal horn forming a state of central hyper excitability (Attal and Bouhassira, 1999; Bolay and Moskowitz, 2002).

Collateral fibers from intact adjacent sensory axons in the skin into denervated areas may occur. Additionally, the nerve endings of damaged PAF may sprout with formation of neuromas which are aberrant patterns of peripheral nerve fibers, a source with altered functional properties (ectopic firing occurring both spontaneously and in response to stimulation) (Amir and Devor, 1993; Devor *et al.*, 1992).

Central Processes in Neuropathic Pain

Under normal circumstances, a painful stimulus results in the release of excitatory amino acids (glutamate, aspartate), neurotrophins e.g. BDNF and peptides (such as Substance P, Neurokinin A and CGRP) from the central terminals of nociceptive fibers in the dorsal horn. BDNF activates tyrosine kinase receptors. Substance P and Neurokinin A interact with the Neurokinin 1 and 2 receptors, respectively and contribute to the induction of dorsal horn sensitization. CGRP causes a Ca^{2+}-influx (L-type VDCC), retards the metabolism of Substance P, and increases the release of Substance P and Excitatory Amino Acids (EAAs) (Naik *et al.*, 2006). Thus, CGRP is the main factor in the hypersensitisation of dorsal horn neurons resulting in chronic pain.

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The EAAs (especially glutamate) interact with receptor subtypes (presynaptic and postsynaptic second order neurons) including ionotropic receptors such as AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), NMDA (N-methyl-D-asparate), and Kainate as well as metabotropic receptors **(**Bolay and Moskowitz, 2002; Costignan and Woolf, 2000**)**. A persistent noxious stimulus causes a conditioning cascade on NMDA receptors for glutamate leading to the removal of the Mg^{2+} ion plug that causes hypersensitivity of CNS neurons for a prolonged period. As a result, sub-threshold noxious input can activate postsynaptic second-order neurons. Central sensitization manifests as an exaggerated or amplified response to noxious stimuli (hyperalgesia), a spread of pain sensitivity beyond the site of injury (secondary hyperalgesia), and as a reduced threshold for eliciting pain. Furthermore, C-fiber input initiates a progressive increase in excitability during the course of the stimulus (wind up of action potential discharge). Once this windup phenomenon is initiated, blockade of peripheral nociceptive input may not completely stop dorsal horn neurons from firing (Woolf, 2004). After peripheral nerve injury Central Nervous System glial cells in the dorsal horn are activated by TNF α - and IL-6 and release proinflammatory mediators that modulate pain processing by affecting either presynaptic release of neurotransmitters and/or postsynaptic excitability. Additionally, neurotrophins such as NGF, BDNF are released, all responsible for enhancing the pain. Thus, following microglial activation, a self-propagating mechanism of enhanced cytokine expression is initiated, responsible for a cascade of inflammatory responses in the central nervous system. Activated glia increase the release of nociceptive neurotransmitters and increase the excitability of nociceptive second-order neurons creating widespread nociceptive changes in the spinal cord.

Along with the above processes, a marked suppression of the inhibitory mechanisms such as the GABA-ergic and opioid receptor mediated analgesia, which leads to an elevated expression of the excitatory reactions causing hyperalgesia, allodynia etc.

Conclusion

Diseases affecting the somatosensory nervous system are the cause of neuropathic pain. Neuropathic pain is also referred as nerve pain as this pain is the result of damage to nerves itself. Determining the cause of neuropathic pain and reversing its effect is an uphill task. Anti convulsant and anti depressant drugs are primarily used as first line of treatment. However, the effective treatment protocol for the neuropathic pain can be formulated if its mechanism is fully understood. Therefore, the current scenario demands extensive studies in this area determining the cause of this pathologic condition as well as treatment methods to be followed to reversal the effect.

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