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Neuropathic Pain: A Complex Pathophysiology of Chronic Pain

Nagare Santosh G.
Pharmacology (IIT, Varanasi)

***Abstract:** As we know that pain is the most common reason for which the 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 be healed 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 healing property so pain mediated through CNS are generally chronic in nature. Even the smallest stimulation results in spontaneous intense pain after than 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 current pharmacological modalities to treat neuropathic pain.*

I. STEPS IN NEURONAL SIGNAL PROCESSING

The 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 pain, there is a 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 due to signal it may recruit other silent receptors so that pain gets amplified this phenomenon called Hyperalgesia. These afferent neurons sensitization blocked by morphine by hyperpolarizing afferent neurons[2]. Neurons of this phase are termed as 1st 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.

a) *C- Fibers*

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

b) *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 required to initiate and transmit the noxious signal. Because they require high potential to activate called as High Threshold Mechanoreceptors.
- Some delta fibers respond to thermal stimuli also termed the Mechano-thermal receptor.
- Neurons of this phase termed as second-order neurons and sensitization of these neurons called central sensitization lead to hyperalgesia and allodynia later.

3) *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.

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

The distinct mechanism of Descending pain inhibitory pathways:

- Descending neurons have direct contact with pain relay neurons of the spinal cord so electrical stimulation of brainstem causes hyperpolarization of nociceptive receptors in the spinal cord and release of neurotransmitters in descending pathway produces the inhibitory effect on ascending pathway so pain signal gets blocked at spinal level[6].
- The central terminal of primary afferent neurons lies in the spinal cord and the central nociceptive receptor for neurotransmitter release in the spinal cord only by descending axon. In relation to this postsynaptic response evoked by dorsal root at lamina 2 reduced by NE.
- Superficiual laminas of the spinal cord contain interneurons which contain inhibitory neurotransmitter like GABA, Glycine, Enkephalin. The descending pathway excites these interneurons of the spinal dorsal horn this will inhibit the ascending pain signal.

4) *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[7]. The opioids are only able to inhibit pain perception no other drug able to do this.

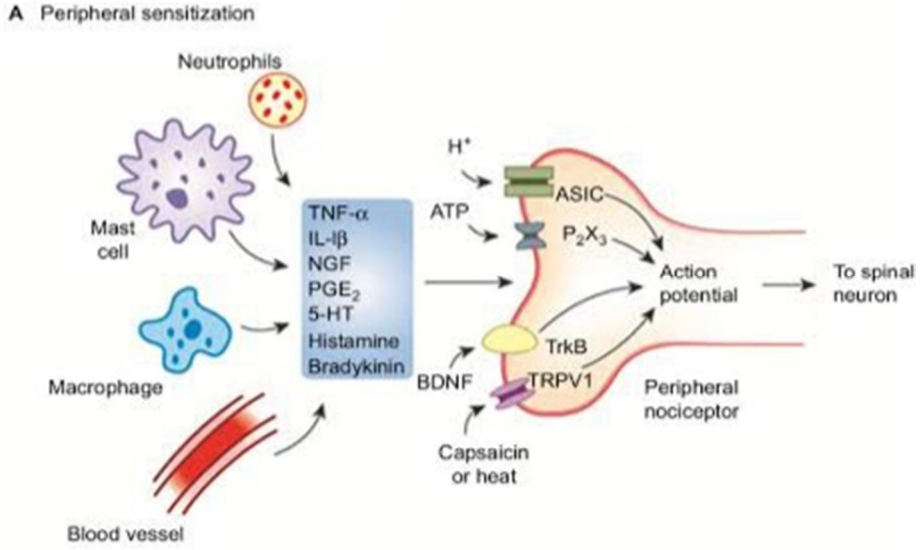
II. PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

Diseases which causes spinal cord lesion are spinal cord injury, syringomyelia, multiple sclerosis, transverse myelitis, and neuromyelitis optica[8]. Peripheral neuropathies diabetes mellitus, HIV[9], and Leprosy, chemotherapy, immune and inflammatory disorder. Because of peripheral nerve lesion, there is an alteration in electrical properties of the sensory nerve which creates the imbalance between the central excitatory and inhibitory system leads to complexity and chronic neuropathic pain.

A. Peripheral Sensitization

This means the sensitization 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 the expression of mRNA to increase the population of the voltage-gated sodium channel. This increase in the population of voltage-gated sodium channel leads to a 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[10]. 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[11]. Damage to peripheral nerve leads to the upregulation of various receptor proteins which are expressed in very less quantity in normal physiology[12] Ex. Vanilloid receptor (TRPV1), TRPV4. There are shreds of evidence that uninjured fibers also contribute to the pain signaling with injured fibers[13]. Product Such as nerve growth factors 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[14].

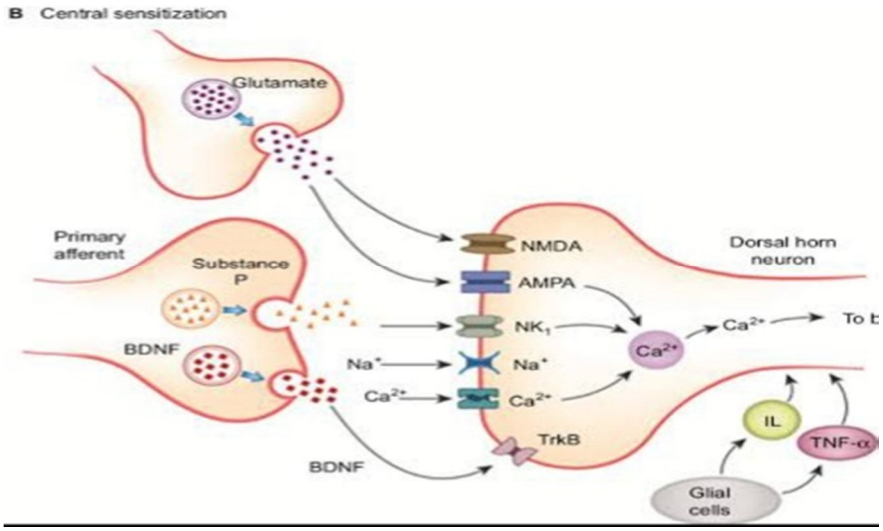
Peripheral sensitization[15]:



B. 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 the excitability of wide dynamic range neurons (WDRN). Wide dynamic range neurons are the neurons that respond to both painful and non- painful stimuli[16]. These neurons behave or work in graded response means as strength of noxious stimulus results in increased pain sensation[17]. 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[18]. Central sensitization is maintained by an intracellular cascade of mitogen-activated protein kinase (MAPK)[19]. 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[20]. 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[21].

Central Sensitization



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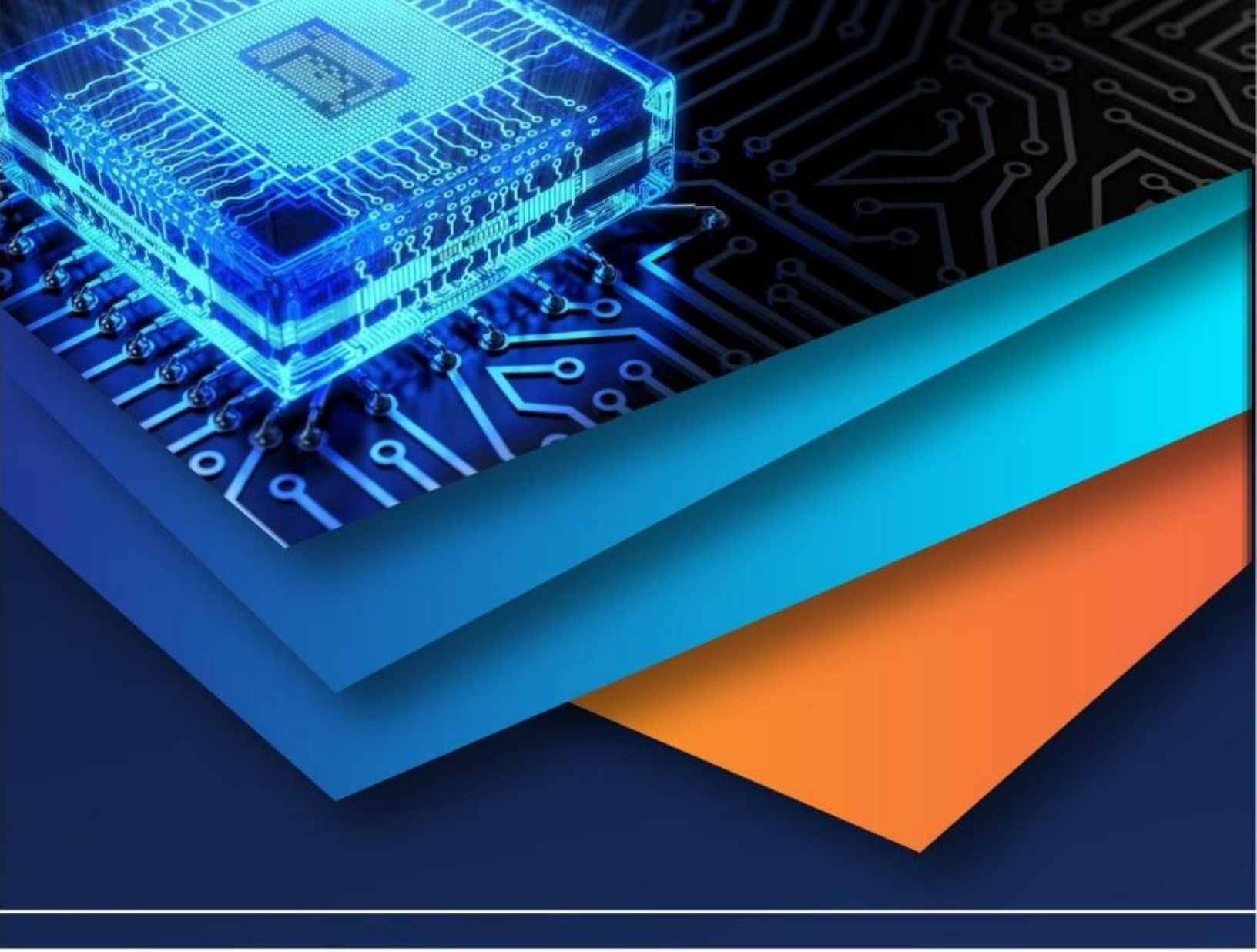

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