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Neuropathic Pain: mechanisms and their clinical implications

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ABSTRACT

Neuropathic pain can develop after nerve injury, when deleterious changes occur in injured neurons and along nociceptive and descending modulatory pathways in the central nervous system. The myriad neurotransmitters and other substances involved in the development and maintenance of neuropathic pain also play a part in other neurobiological disorders. This might partly explain the high comorbidity rates for chronic pain, sleep disorders, and psychological conditions such as depression, and why drugs that are effective for one condition may benefit others. Neuropathic pain can be distinguished from non-neuropathic pain by two factors. Firstly, in neuropathic pain there is no transduction (conversion of a nociceptive stimulus into an electrical impulse). Secondly, the prognosis is worse: injury to major nerves is more likely than injury to non-nervous tissue to result in chronic pain. In addition, neuropathic pain tends to be more refractory than non-neuropathic pain to conventional analgesics, such as non-steroidal anti-inflammatory drugs and opioids. However, because of the considerable overlap between neuropathic and nociceptive pain in terms of mechanisms and treatment modalities, it might be more constructive to view these entities as different points on the same continuum. This review focuses on the mechanisms of neuropathic pain, with special emphasis on clinical implications.

ANALYSIS

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Background Information

Pain is a survival mechanism that serves as a warning sign of ongoing or impending tissue damage. Pain is also, however, one of the most prevalent human conditions, with some estimates concluding that up to 1/3 of the population experience chronic pain (1-3). Up to 20% of those who report chronic pain are thought to have predominantly neuropathic pain (2, 3). This high prevalence is blamed largely on the lack of effective treatment options for patients with chronic neuropathic pain. Unlike nociceptive pain, which responds well to anti-inflammatory or opioid medications, neuropathic pain is typically non-responsive to traditional analgesic treatments, as these medications are unable to target the underlying mechanisms of neuropathic pain.

Further complicating matters is the fact that the mechanisms underlying neuropathic pain are often difficult to identify. This review provides information for clinicians regarding what is currently understood about neuropathic pain and its causative mechanisms, in an effort to help steer future research and guide clinical practice.

SUMMARY

Physiology and Classification

Pain can be broadly defined as nociceptive or neuropathic. Nociceptive pain tends to be either somatic or, less often, visceral, and results from damage or degenerative changes. Neuropathic pain, conversely, results from injury to, or dysfunction in, the somatosensory system itself (4). In neuropathic pain, tissue damage directly affects the nervous system, bypassing the usual first stage of pain generation – transduction. The result is the generation of ectopic discharges, which perpetuate the pain signals. While nociceptive pain may be associated with evolutionary benefits, neuropathic pain is always maladaptive.

Emotional vs. Physiological Aspects

A common misconception is that pain is purely a physiological phenomenon. It is, in fact, an integrative package, consisting of neurophysiological processes as well as contextual, psychological, and sociocultural factors. This multi-factorial nature of pain helps to explain the discrepancies often noted between preclinical studies and clinical studies, which assess analgesic efficacy, and clinical practice, where overall effectiveness is measured. It is because of these interacting factors that the intensity of pain often correlates poorly with the degree of pathology, especially for conditions such as low back pain (5).

This multi-factorial nature of pain helps to explain the effect of psychosocial factors such as depression in chronic pain. It also helps to explain the contextual nature of pain as a human experience, where the setting and context of an injury and/or pain has an impact on the tolerance level of individual patients.

Several mechanisms are responsible for the creation and perpetuation of chronic pain. These mechanisms include peripheral, spinal and supra-spinal mechanisms – subtypes of each will be discussed below.

Peripheral Mechanisms

Peripheral Sensitization

A natural first step in the injury process is that of peripheral sensitization, where inflammation and reparatory processes lead to a state of hyper-excitability. In most patients, this state resolves as healing occurs and inflammation subsides. However, when nociception persists because of repeated stimulation from ongoing injury or disease (for example, in diabetes), the changes in primary afferent neurons may persist.

Chronic pain can evolve from these changes to afferent neurons and from non-synaptic "cross-talk" (ephaptic transmission – 'The phenomenon by which two independent nerves communicate with each other through an artificial synapse, which often develops after injury to the insulating myelin sheath that normally prevents crosstalk between parallel nerves'), which can lead to allodynia (pain produced by non-painful stimulus) and hyperalgesia (exaggerated pain perception). Both result from either damage or incorrect stimulation of nociceptors and represent the central problem in treating neuropathic pain; namely, the difficulty in adequately addressing the causative mechanisms.

Sympathetically Maintained Pain
Pain enhanced or maintained by an abnormality in the sympathetic nervous system is known as sympathetically maintained pain. This type of pain is classically represented by complex regional pain syndrome, where the interaction between the sympathetic nervous system and the somatosensory system perpetuates pain. Such conditions are clinically identified by temperature or colour changes in an affected extremity, swelling or atrophy, and pain worsened by cold. Nerve blocks are often utilized in an attempt to control this chronic pain but again fall victim to the inability of analgesics to address the causative mechanisms.

Spinal Mechanisms

Spinal Glutamatergic Regulation
Peripheral nerve injury increases neuronal excitability in the spinal cord by activating excitatory glutamate receptors (6). In clinical practice, the use of NMDA receptor antagonists to prevent opioid tolerance and hyperalgesia has been disappointing, as has the use of these drugs to treat chronic neuropathic pain.

Glial Activation and Pro-Inflammatory Cytokines
Pro-inflammatory cytokines such as interleukin-1β, IL-6 and tumour necrosis factor are produced in response to nerve injury. In addition to an important role in the inflammatory process, these cytokines play a key role in sensitization of the central nervous system and may contribute to allodynia and hyperalgesia.

Glial cells comprise about 70% of the central nervous system and play an important role in maintenance and homeostasis. When activated, glial cells stimulate the immune system and release cytokines, chemokines and cytotoxic substances that contribute to the inflammatory effect in chronic pain.

Supraspinal Mechanisms

In patients with neuropathic pain, cortical reorganization occurs after injury, and the extent of the changes seems to correlate with the degree of pain. Changes that occur in supraspinal regions may explain the strong association between neuropathic pain and mood disorders. In fact, chronic pain patients have been shown to have less gray matter than control patients (7).

Disinhibition

Spinal Cord Level
Descending inhibition refers to the series of events resulting in the activation of inhibitory neurons that attenuate pain following transmission of nociceptive stimulus to higher cortical centres. After nerve injury, a loss of inhibitory currents occurs, which has been shown to provoke tactile allodynia and hyperalgesia (8). Descending inhibition plays an important role in determining how people experience pain and can be both inhibitory and facilitory in nature. The balance between inhibition and amplification is dynamic and influenced by context, behavior, emotions, expectations, timing, and pathology, further complicating the treatment and assessment process.

Supraspinal Level
After nerve injury, several processes take place that mitigate the normal pain attenuating pathways. These include a shift from a predominantly inhibitory role to a facilitative function and a reduction in tonic noradrenergic inhibition. The ability of neurotransmitters in these processes to affect pain, mood and sleep may help to explain the high comorbidity rates noted among pain, depression, anxiety and sleep disturbances.

Neuropathic vs. Nociceptive Pain
Two main factors currently distinguish nociceptive pain from neuropathic pain:

1. Nociceptive pain requires transduction to convert a non-electrical signal (for example, mechanical) to an electrochemical one, whereas neuropathic pain involves direct nerve stimulation.
2. Differing prognosis: most people with nociceptive pain (for example, after surgery) recover, but injury to a major nerve (for example, plexopathy or limb amputation) often results in persistent pain.

However, the growing consensus is that considerable overlap exists between neuropathic and nociceptive pain. That is, the shared pathophysiological mechanisms and overlap in response to treatment, warrants a consideration that the different types of chronic pain be viewed as points on the same continuum.

Emerging Treatments
Several emerging developments must unfold to improve our understanding of chronic pain and its treatment options. These include:

- New animal models should account for the influence of clinical comorbidities such as depression on nociceptive behaviors.
- Behavioral assessment tools should be capable of measuring the various dimensions of pain experiences.
- The association between brain reorganization seen on advanced imaging and the chronicity of pain should be further explored.
- The identification of biomarkers and the genotyping or phenotyping of pain characteristics may provide tools that enable us to understand better the heterogeneity of clinical pain, while formulating individualized treatment regimens.

CLINICAL APPLICATION & CONCLUSIONS

Injury to the peripheral or central nervous system results in maladaptive changes in neurons along the nociceptive pathway that can cause neuropathic pain. There is considerable overlap between neuropathic and nociceptive pain pathways; however, implementing a treatment plan aimed at addressing the mechanisms of pain is exceedingly difficult in neuropathic pain. As a result, chronic pain has itself become considered a "disease", with an associated socioeconomic concern that requires urgent clinical and research attention.

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