Neuropathic Pain

When Nerve Lesion Turns off Peripheral Analgesia

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Peripheral nerve injury often leads to the development of neuropathic pain that manifests itself in the form of abnormal pain hypersensitivity such as allodynia and hyperalgesia. Pain from damaged or diseased nerves is common worldwide and affects up to 6% of the population. The abundant literature dealing with the physiopathologic mechanisms of this disease define numerous alterations in the dorsal root ganglia (DRG) and in the spinal cord and supraspinal structures. These alterations, involving multiple cellular partners, include increased release of pronociceptive molecules, change in gene expression, and remodeling of neural networks. This leads to hyperexcitability of primary nociceptive afferents within the periphery and reorganization of neural networks in the central nervous system. Numerous protein candidates have been suggested as critical for the development of chronic neuropathic pain. However, treatment of neuropathic pain remains unsatisfactory due to the lack of effective pain medications. Importantly, opioids such as morphine cause multiple side effects and have societal consequences. The new report by Zhang et al., is of high interest as it enhances our understanding of the dysregulations that operate after nerve lesion by reporting epigenetic regulation leading to defective endogenous pain inhibition and limited morphine effectiveness. This study may open up novel interventional therapies for the management of neuropathic pain.

Epigenetic Regulation Governs Peripheral Neuropathic Pain

Over the last decade, epigenetic regulation has been extensively studied in order to understand the complex interplay between an organism and its environment on gene expression. Epigenetics refers to the processes that govern trait variations without changes in genomic DNA sequence. DNA methylation, histone acetylation, and protein arginine methyltransferases.

“In an animal model of neuropathic pain…epigenetic regulation [can lead] to defective endogenous pain inhibition and limited morphine effectiveness.”

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Fig. 1. Hypothetical view of epigenetic $\mu$-opioid receptor (MOR) gene repression in neuropathic pain condition. The activation of the methyltransferase suppressor of variegation 3-9 homolog 1 (SU39H1) after nerve injury produces the transfer of methyl group on lysine located on histone H3. That facilitates chromatin compaction (heterochromatin) limiting access of transcription factors to specific DNA sequence. That could lead to decreased MOR gene expression in the dorsal root ganglia. M = methylation group.

L5 lesion produces overexpression of neuronal SU39H1 in the DRG and in the dorsal horn of the spinal cord. Remarkably, inhibition of SU39H1 via the administration of SU39H1 inhibitor or via siRNA reduced nerve injury–induced pain-related behaviors. The method they used to evaluate the behavioral consequences of such an inhibition is particularly elegant. The authors not only used the stimulus-evoked withdrawal reflex with the classical nociceptive tests, but also evaluated ongoing pain as measured by a place preference paradigm, a more sophisticated pain test that has been shown to be more predictive of drug effectiveness in humans. Interestingly, this study is the first to show that inhibition of SU39H1 in DRG reduces central pain sensitization as evidenced by the decreased expression of phosphorylated extracellular signal–regulated kinase 1/2 and glial fibrillary acidic protein. This suggests that targeting processes governing the regulation of gene expression impact the spinal changes leading to pain sensitization. Thus, the behavioral analysis associated with cellular approaches clearly identified the methyltransferase as an important factor in the development of neuropathic pain–related behaviors.

Is Neuropathic Pain Mainly due to Long-term Alteration in Endogenous Pain Inhibition?

The report by Zhang et al. confirms the previous reports by Ueda and coworkers, showing that chronic nerve lesion induces decreases in opioid receptors, leading to poor effectiveness of opioid treatment such as morphine. Recently, similar epigenetic regulation of $\mu$-opioid receptor (MOR) expression has been provided, showing that inhibition of the methyltransferase G9a blocks nerve injury–induced decreased MOR expression and potentiates morphine-induced analgesia. Altogether, these data strongly suggest that MOR expression is tightly regulated after nerve injury by complex epigenetic modifications (fig. 1). Interestingly, inhibition of SU39H1 is sufficient to fully restore MOR expression in the DRG without affecting G9a expression. This suggests that SU39H1 activation is critical for the down-regulation of MOR expression produced by nerve injury. Further investigations are now necessary to understand the complex genetic interplay regulating MOR expression after nerve injury.

The current study by Zhang et al. further bolsters the case that peripheral nerve injury causes an imbalance between excitation and inhibition. It is well understood that nociception is controlled by both pain facilitatory and pain inhibitory systems. Chronic neuropathic pain is accepted to be associated with an overactivation of pain facilitatory systems triggering by neuroimmune interactions and a decreased activation of pain inhibitory systems. The current study is interesting in this way since molecular changes, i.e., epigenetic regulation, have been shown to affect pain inhibition leading to persistent nociceptive hypersensitivity. Epigenetic alterations of endogenous pain systems can also be exemplified through the histone hypoacetylation at the Gad2 promoter in a brainstem structure, the nucleus raphe magnus emphasizing that epigenetic regulation takes place not only in primary sensory neurons and spinal cord but also in supraspinal sites. Therefore, epigenetic mechanisms decreasing GAD65 and/or MOR expression would create an imbalance biasing toward neuronal excitability, ultimately leading to the worsening of neuropathic pain.

Peripheral Analgesia for the Treatment of Neuropathic Pain

What is the clinical significance of such a study? First, and most of clinicians will agree, opioids especially MOR agonists are not the accepted standard for the management of peripheral neuropathic pain. By demonstrating the epigenetic silencing of MOR in the DRG, Zhang et al. brings some striking evidence for the lack of peripheral efficacy of MOR agonists to reduce nerve injury–induced pain hypersensitivity, limiting the interest for the use of opioids alone in the management of peripheral neuropathic pain. Efforts are still needed to clearly establish such a phenomenon in humans to give clear recommendation regarding the treatment of peripheral neuropathic pain. Actually, the results obtained by the authors strongly support the use for combinatorial intervention associating SUV39H1 inhibitor and opioids. This multimodal approach would not only rescue opioid analgesia but also reduce opioid consumption, limiting the development of adverse effects. Second, the authors showed that the administration of methylsalicylonitrosamide, an opioid antagonist that does not cross the blood–brain barrier, completely reverses the antihyperalgesic effects of SUV39H1 siRNA, suggesting the existence of an effective peripheral analgesia to reverse nerve injury–induced pain–related behaviors. This strongly supports that blockade of DRG epigenetic alterations is sufficient to restore endogenous peripheral...
pain inhibition counteracting the overactivation of primary sensory neurons produced by nerve injury. Peripheral intervention at the level of primary sensory neurons is shown to effectively reduce pain hypersensitivity associated with nerve injury. Thus, one could speculate that the development of peripherally acting SUV39H1 inhibitors associated with peripherally acting MOR agonists may represent an effective and safe strategy for the management of peripheral neuropathic pain.

Patients suffering from neuropathic pain lack effective therapies despite newer treatment modalities. Understanding epigenetic mechanisms regulating gene expression is crucial to advancing our knowledge regarding the long-lasting changes responsible for persistent neuropathic pain. The road ahead is still long, and much work needs to be done before we can envisage proposing new therapeutics targeting epigenetic systems to clinicians. However, by showing that epigenetic DRG-targeted intervention restores peripheral analgesia, Zhang et al., opens up an important research avenue with translational potential. Indeed, targeting epigenetic dysregulation via pharmacologic intervention and thereby modifying DRG cellular function could provide innovative and safe regional analgesia to blunt nociceptive sensitization and will likely change the approach toward management of peripheral neuropathic pain.

Competing Interests
The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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