Opinion

Biology

The Role of the Immune System in Nociception Development

A Neuroimmune Perspective

Heinz Martin Grimm*

University of Bonn, Regina-Pacis-Weg 3, 53113 Bonn, Germany
*: All correspondence should be sent to: Dr. Heinz Martin Grimm
Author's Contact: Heinz Martin Grimm, Ph.D., E-mail: hmgrimm@gmail.com
DOI: https://doi.org/10.15354/si.25.op269
Funding: No funding source declared.
COI: The author declares no competing interest.
AI Declaration: The author affirms that artificial intelligence did not contribute to the process of preparing the work.

Nociception, the neural process responsible for detecting and transmitting pain signals, was historically perceived as a purely neuronal phenomenon. It primarily involved nociceptors—specialized sensory neurons located in peripheral tissues—that detect potentially harmful stimuli and convey this information to the central nervous system. However, a growing body of evidence over the past two decades has illuminated the pivotal role of the immune system in modulating nociception at both peripheral and central levels. This neuroimmune interplay has profound implications for understanding the pathophysiology of acute and chronic pain and opens novel therapeutic avenues for managing complex pain conditions.

Keywords: Nociception; Immune System; Neuronal Connection; Endocrinology; Pain

Science Insights, April 30, 2025; Vol. 46, No. 4, pp.1795-1798.

THE immune system plays a crucial role in nociception development. Nociception is the physiological process of detecting noxious stimuli and transmitting signals to the brain that are interpreted as pain (Pinho‐Ribeiro et al., 2016). Immune cells, such as microglia and T cells, have been shown to interact with neurons in the spinal cord and play a key role in regulating pain sensitivity. When tissues are damaged, immune cells release cytokines and chemokines that activate nociceptive neurons, leading to the perception of pain. Additionally, research has demonstrated that chronic inflammation can lead to hyperalgesia, an increased sensitivity to pain (Uvnäs-Moberg et al., 2024). Understanding the complex interplay between the immune system and nociception is essential for developing effective treatments for chronic pain conditions. This knowledge can facilitate the development of targeted therapies that modulate immune responses and alleviate pain without causing unwanted side effects.

Peripheral Immune Regulation of Nociception

The immune system contributes significantly to the initiation and amplification of nociceptive signaling through the release of inflammatory mediators in response to tissue injury or infection. In the periphery, resident and recruited immune cells—including macrophages, mast cells, neutrophils, and dendritic cells—release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleu-

kin-6 (IL-6) (Gu et al., 2024). These mediators enhance the sensitivity of nociceptors, a phenomenon known as peripheral sensitization.

These cytokines exert their effects by modifying the activity of ion channels expressed on nociceptors, including transient receptor potential vanilloid 1 (TRPV1), acid-sensing ion channels (ASICs), and voltage-gated sodium channels like Nav1.7 and Nav1.8 (Bhave & Gereau, 2004). For example, IL-1β has been shown to increase TRPV1 expression, lowering the threshold for heat activation and contributing to thermal hyperalgesia (Cheng & Ji, 2008). Similarly, prostaglandins produced by cyclooxygenase enzymes sensitize nociceptors to mechanical stimuli, amplifying the pain response (Jang & Garraway, 2024). In addition, immune-derived growth factors such as nerve growth factor (NGF) promote nociceptor sensitization and sprouting, enhancing the density of innervation in inflamed tissues (Fiore et al., 2023). The combined action of these mediators contributes to the cardinal symptoms of inflammatory pain: redness, swelling, heat, and, notably, pain.

Central Immune Regulation of Nociceptive Processing

While peripheral sensitization accounts for heightened pain at the site of injury, central sensitization describes the increased excitability of spinal and supraspinal neurons that process nociceptive input. Glial cells—especially microglia and astrocytes—play a crucial role in mediating central sensitization via neuroimmune mechanisms (Karavis et al., 2023).

Following peripheral nerve injury or sustained nociceptive input, microglia in the dorsal horn of the spinal cord become activated and undergo morphological and functional changes. Activated microglia release cytokines (e.g., IL-1β, TNF-α), chemokines (e.g., CCL2), and neurotrophic factors like brain-derived neurotrophic factor (BDNF) that modulate synaptic transmission (Jayathilake et al., 2025). BDNF, in particular, reduces inhibitory GABAergic signaling by altering the chloride gradient in dorsal horn neurons, thus facilitating the excitability of pain-transmitting neurons (Mackey et al., 2025).

Astrocytes, the most abundant glial cells in the CNS, also contribute to chronic pain by maintaining a pro-inflammatory environment (Wu et al., 2024). Once activated, they release cytokines and gliotransmitters (e.g., glutamate, ATP) that support persistent nociceptive signaling (Marty-Lombardi et al., 2024). Notably, glial activation tends to persist beyond the resolution of the initial injury, providing a cellular basis for chronic pain conditions (Jang & Garraway, 2024).

Adaptive Immunity and Chronic Pain

Although innate immune cells are primarily involved in acute nociceptive responses, adaptive immune cells—including T and B lymphocytes—play a significant role in chronic pain states. CD4+ T cells infiltrate the injured peripheral nerves and spinal cord, producing IFN-γ and IL-17, which further stimulate glial activation and perpetuate inflammation (Marty-Lombardi et al., 2024). Th17 cells, in particular, have been associated with autoimmune neuropathies and inflammatory pain.

In contrast, regulatory T cells (Tregs) serve a protective, anti-nociceptive function. They limit immune activation and inflammation through the secretion of anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β). Experimental depletion of Tregs exacerbates neuropathic pain in murine models, whereas their adoptive transfer or pharmacological expansion alleviates pain symptoms (Jayathilake et al., 2025). This dichotomy highlights the dualistic role of adaptive immunity in either exacerbating or mitigating pain depending on immune context and balance.

Autoantibody-mediated pain also underscores the role of adaptive immunity in nociception. In conditions like rheumatoid arthritis, systemic lupus erythematosus, and complex regional pain syndrome, autoantibodies target neuronal or glial antigens, leading to neuroinflammation and pain independent of tissue damage (Karcz et al., 2024).

Neuroimmune Crosstalk

The complex interplay between the immune and nervous systems is facilitated by shared signaling molecules and bidirectional communication. Nociceptors express receptors for cytokines, chemokines, and immune-derived growth factors, while immune cells express receptors for neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) released by neurons (Yi et al., 2024). This neuroimmune crosstalk is not only pivotal in amplifying pain but also in regulating immune responses based on neural activity.

This reciprocal relationship forms a feedback loop: immune activation leads to neuronal sensitization, and neuronal activity, in turn, can recruit and activate immune cells (Grace et al., 2014). This loop is especially relevant in chronic pain conditions, where low-grade neuroinflammation becomes self-sustaining.

Therapeutic Implications

Recognizing the immune system as a key modulator of nociception suggests promising therapeutic targets beyond traditional analgesics. Biologics targeting cytokines such as TNF-α (e.g., etanercept), IL-6 (e.g., tocilizumab), and IL-1β (e.g., anakinra) have demonstrated analgesic effects in inflammatory and autoimmune conditions, sometimes independent of their anti-inflammatory action (Sommer et al., 2017). Inhibiting glial activation with minocycline or modulating microglial BDNF release may also attenuate central sensitization (Chen et al., 2018).

Moreover, harnessing Treg biology to promote immune tolerance and resolution of neuroinflammation offers a novel strategy for chronic pain management. Small molecules or biologics that enhance Treg function are currently under investigation for autoimmune diseases and may have potential in chronic pain therapy (Nijs et al., 2021).

Conclusion

Nociception is no longer viewed solely as a neuronal event but as a dynamic neuroimmune process involving intricate interactions between immune cells, cytokines, and nociceptive pathways. Immune cells shape both peripheral and central mechanisms of pain through the release of pro- and anti-inflammatory mediators, influencing the trajectory of pain from acute to chronic. Understanding these interactions expands the conceptu-

al framework of pain physiology and paves the way for innovative, immune-targeted analgesic therapies. As research continues to unravel the complexity of neuroimmune crosstalk, it brings us closer to precision-based treatments for the millions suffering from persistent pain disorders. ■

Received: March 06, 2025 | Revised: March 18, 2025 | Accepted: April 3, 2025

References

Bhave, G., & Gereau, R. W. (2004). Posttranslational mechanisms of peripheral sensitization. Journal of Neurobiology, 61(1), 88–106. https://doi.org/10.1002/neu.20083

Chen, G., Zhang, Y., Qadri, Y. J., Serhan, C. N., & Ji, R. (2018). Microglia in Pain: Detrimental and protective roles in pathogenesis and resolution of pain. Neuron, 100(6), 1292–1311. https://doi.org/10.1016/j.neuron.2018.11.009

Cheng, J., & Ji, R. (2008). Intracellular signaling in primary sensory neurons and persistent pain. Neurochemical Research, 33(10), 1970–1978. https://doi.org/10.1007/s11064-008-9711-z

Fiore, N. T., Debs, S. R., Hayes, J. P., Duffy, S. S., & Moalem-Taylor, G. (2023). Pain-resolving immune mechanisms in neuropathic pain. Nature Reviews Neurology. https://doi.org/10.1038/s41582-023-00777-3

Grace, P. M., Hutchinson, M. R., Maier, S. F., & Watkins, L. R. (2014). Pathological pain and the neuroimmune interface. Nature Reviews. Immunology, 14(4), 217–231. https://doi.org/10.1038/nri3621

Gu, D., Xia, Y., Ding, Z., Qian, J., Gu, X., Bai, H., Jiang, M., & Yao, D. (2024). Inflammation in the Peripheral Nervous System after Injury. Biomedicines, 12(6), 1256. https://doi.org/10.3390/biomedicines12061256

Jang, K., & Garraway, S. M. (2024). A review of dorsal root ganglia and primary sensory neuron plasticity mediating inflammatory and chronic neuropathic pain. Neurobiology of Pain, 15, 100151. https://doi.org/10.1016/j.ynpai.2024.100151

Jayathilake, N. J., Phan, T. T., Kim, J., Lee, K. P., & Park, J. M. (2025). Modulating neuroplasticity for chronic pain relief: noninvasive neuromodulation as a promising approach. Experimental & Molecular Medicine. https://doi.org/10.1038/s12276-025-01409-0

Karavis, M. Y., Siafaka, I., Vadalouca, A., & Georgoudis, G. (2023). Role of microglia in neuropathic pain. Cureus. https://doi.org/10.7759/cureus.43555

Karcz, M., Abd-Elsayed, A., Chakravarthy, K., Aman, M. M., Strand, N., Malinowski, M. N., Latif, U., Dickerson, D., Suvar, T., Lubenow, T., Peskin, E., D'Souza, R., Cornidez, E., Dudas, A., Lam, C., Farrell, M., II, Sim, G. Y., Sebai, M., Garcia, R., . . . Deer, T. (2024). Pathophysiology of Pain and Mechanisms of Neuromodulation: A Narrative Review (A Neuron Project). Journal of Pain Research, Volume 17, 3757–3790. https://doi.org/10.2147/jpr.s475351

Mackey, S., Aghaeepour, N., Gaudilliere, B., Kao, M., Kaptan, M., Lannon, E., Pfyffer, D., & Weber, K. (2025). Innovations in acute and chronic pain biomarkers: enhancing diagnosis and personalized therapy. Regional Anesthesia & Pain Medicine, 50(2), 110–120. https://doi.org/10.1136/rapm-2024-106030

Marty-Lombardi, S., Lu, S., Ambroziak, W., Schrenk-Siemens, K., Wang, J., DePaoli-Roach, A. A., Hagenston, A. M., Wende, H., Tappe-Theodor, A., Simonetti, M., Bading, H., Okun, J. G., Kuner, R., Fleming, T., & Siemens, J. (2024). Neuron–astrocyte metabolic coupling facilitates spinal plasticity and maintenance of inflammatory pain. Nature Metabolism, 6(3), 494–513. https://doi.org/10.1038/s42255-024-01001-2

Nijs, J., George, S. Z., Clauw, D. J., Fernández-De-Las-Peñas, C., Kosek, E., Ickmans, K., Fernández-Carnero, J., Polli, A., Kapreli, E., Huysmans, E., Cuesta-Vargas, A. I., Mani, R., Lundberg, M., Leysen, L., Rice, D., Sterling, M., & Curatolo, M. (2021). Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. The Lancet Rheumatology, 3(5), e383–e392. https://doi.org/10.1016/s2665-9913(21)00032-1

Pinho-Ribeiro, F. A., Verri, W. A., & Chiu, I. M. (2016). Nociceptor Sensory Neuron–Immune interactions in pain and inflammation. Trends in Immunology, 38(1), 5–19. https://doi.org/10.1016/j.it.2016.10.001

Sommer, C., Leinders, M., & Üçeyler, N. (2017). Inflammation in the pathophysiology of neuropathic pain. Pain, 159(3), 595–602. https://doi.org/10.1097/j.pain.0000000000001122

Uvnäs-Moberg, K., Gross, M. M., Calleja-Agius, J., & Turner, J. D. (2024). The Yin and Yang of the oxytocin and stress systems: opposites, yet interdependent and intertwined determinants of lifelong health trajectories. Frontiers in Endocrinology, 15. https://doi.org/10.3389/fendo.2024.1272270

Wu, M., Song, W., Zhang, M., Teng, L., Tang, Q., & Zhu, L. (2024). Potential mechanisms of exercise for relieving inflammatory pain: a literature review of animal studies. Frontiers in Aging Neuroscience, 16. https://doi.org/10.3389/fnagi.2024.1359455

Zou, Y., Liu, C., Wang, Z., Li, G., & Xiao, J. (2024). Neural and immune roles in osteoarthritis pain: Mechanisms and intervention strategies. Journal of Orthopaedic Translation, 48, 123–132. https://doi.org/10.1016/j.jot.2024.07.010