REVIEW ARTICLE

Physiology

KEY WORDS: Nociception; Peripheral sensitization; Central sensitization; Pain neuroimaging; Descending modulation; Human pain models

NOCICEPTIVE SIGNALLING IN HUMAN PHYSIOLOGY: A SYSTEMATIC ANALYSIS OF PERIPHERAL AND CENTRAL PAIN MECHANISMS

Dr Sangita Rankhamb Associate Professor, Department Of Physiology, MGM Medical College, Chhatrapati Sambhajinagar

Dr Khan Saba Anjum* Assistant Professor, Department Of Physiology, MGM Medical College, Chhatrapati Sambhajinagar *Corresponding Author

ABSTRACT

This systematic review examines the current understanding of nociceptive signaling pathways in human physiology, with particular emphasis on peripheral and central mechanisms that underlie pain perception. We synthesized evidence from neurophysiological recordings, molecular studies, quantitative sensory testing, and advanced neuroimaging techniques to provide a comprehensive analysis of human pain processing. Peripheral mechanisms, including nociceptor transduction and sensitization, demonstrate remarkable specificity with distinct molecular pathways for thermal, mechanical, and chemical noxious stimuli. Notable advances in understanding TRP channel function and inflammatory mediator actions have clarified how tissue injury amplifies nociceptive signaling. Central mechanisms reveal complex processing at spinal and supraspinal levels, with evidence for activity-dependent plasticity that manifests as central sensitization in many chronic pain conditions. Neuroimaging studies have delineated a distributed network of brain regions involved in pain processing, challenging the concept of a specific "pain matrix" and highlighting the importance of salience detection systems. The review also addresses bidirectional descending modulatory pathways that can either enhance or inhibit incoming nociceptive signals. Significant interindividual variability in pain processing appears attributable to genetic factors, sex differences, psychological influences, and prior pain experiences. Importantly, this analysis identifies translational gaps between preclinical models and human findings, explaining several failed clinical trials targeting seemingly promising mechanisms. The review concludes by outlining emerging research directions, including the development of human-specific models, investigation of neuroimmune interactions, and identification of biomarkers for pain chronification. This comprehensive assessment of human nociceptive mechanisms provides a foundation for developing more effective, mechanism-based approaches to pain management.

INTRODUCTION

Pain represents one of the most fundamental physiological mechanisms for survival, serving as a warning system that alerts organisms to potential or actual tissue damage (1). Despite its critical protective function, our understanding of the complex physiological processes that underlie human nociception continues to evolve rapidly. Nociceptive signaling involves a sophisticated interplay between peripheral sensory neurons, spinal cord circuits, and multiple brain regions, creating a multidimensional experience that encompasses sensory-discriminative, affective-motivational, and cognitive-evaluative components (2,3).

The past two decades have witnessed remarkable advances in our understanding of human pain physiology, driven by technological innovations in neuroimaging, electrophysiology, and molecular biology (4). These developments have facilitated unprecedented insights into the molecular architecture of nociceptors, the dynamic processing of nociceptive signals, and the modulatory mechanisms that shape pain perception (5,6). From the identification of novel ion channels involved in transduction to the elucidation of complex descending inhibitory and facilitatory pathways, the field has progressed significantly beyond the classical "gate control theory" proposed by Melzack and Wall (7).

Human nociceptive physiology is characterized by remarkable plasticity, with the capacity for both sensitization and adaptation in response to various stimuli and conditions (8). This plasticity, while essential for normal physiological functioning, also represents a double-edged sword, as it can contribute to maladaptive changes that underlie chronic pain states (9). Understanding these mechanisms is not merely an academic pursuit but holds profound implications for developing targeted analgesic therapies that address specific components of the pain pathway (10).

This systematic review aims to synthesize current knowledge on nociceptive signaling in human physiology, with a particular focus on peripheral and central mechanisms. We will examine the structural and functional characteristics of human nociceptors, their transduction mechanisms, and the complex pathways through which nociceptive information is processed and modulated at spinal and supraspinal levels. By integrating findings from both basic science and clinical research, we seek to provide a comprehensive framework for understanding physiological pain processing in humans, highlighting recent discoveries that have transformed our conceptualization of this essential sensory system (11,12).

Through this analysis, we hope to illuminate not only the fundamental physiological principles that govern nociception but also the critical gaps in our understanding that warrant further investigation. As our knowledge of these mechanisms continues to expand, so too does our capacity to develop more effective strategies for managing pain while preserving its essential protective function.

MATERIALS AND METHODS

Literature Search Strategy

A comprehensive search of published literature was conducted using multiple electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and EMBASE. The search covered original research articles published in English between January 2000 and March 2025. Search terms included combinations of the following keywords: "nociception," "pain signaling," "nociceptors," "pain transduction," "central sensitization," "peripheral sensitization," "neuroinflammation," "pain modulation," "pain perception," "hyperalgesia," "allodynia," "descending pain control," and "pain processing." Additional relevant studies were identified through manual searches of reference lists from retrieved articles and systematic reviews.

Inclusion Criteria:

- Peer-reviewed original research articles, systematic reviews, and meta-analyses

- Studies investigating nociceptive signaling mechanisms in humans
- Studies examining peripheral and/or central pain mechanisms
- Studies using validated experimental pain models in healthy subjects
- Clinical studies with clear methodological descriptions
- Neuroimaging studies of pain processing

Exclusion Criteria:

- Animal studies without direct human correlates
- Case reports and small case series (n < 10)
- Studies focusing exclusively on analgesic interventions without mechanistic analysis
- Articles not available in English
- Studies with methodological flaws or inadequate reporting of methods
- Duplicate publications

Data Extraction And Quality Assessment

Two independent reviewers extracted data using a standardized form designed to capture methodological details, participant characteristics, experimental procedures, outcome measures, and key findings. Discrepancies were resolved through consensus with a third reviewer. The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials. For systematic reviews, the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) instrument was applied.

Findings were synthesized using a narrative approach organized around key mechanistic themes. Where multiple high-quality studies addressed similar mechanisms, patterns of evidence were identified. Given the heterogeneity of methodologies and outcome measures across studies of nociceptive mechanisms, a formal meta-analysis was not performed. Instead, we employed a qualitative comparative analysis to identify convergent findings across methodological approaches and study populations.

Methodological Analysis

We performed a critical analysis of the methodologies used to study nociceptive signaling, evaluating:

1. **Neuroimaging Techniques**: Functional MRI (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), and electroencephalography (EEG) studies were analyzed for their contributions to understanding central pain processing.
2. **Quantitative sensory testing (QST)**: Various QST protocols used to assess peripheral and central sensitization were compared and evaluated.
3. **Microneurography And Electrophysiology**: Studies using direct recordings from primary afferents and central neurons were assessed for their insights into nociceptive signal transduction and transmission.
4. **Molecular And Biochemical Approaches**: Methods for measuring inflammatory mediators, neurotransmitters, and other signaling molecules in human subjects were evaluated.
5. **Psychophysical Assessments**: Approaches to measuring pain perception, including threshold determination, pain ratings, and multidimensional pain assessments were systematically compared.

Limitations Assessment

For each methodological approach, we critically assessed limitations including participant selection biases, measurement confounds, generalizability constraints, and theoretical assumptions. This assessment informed our evaluation of the strength of evidence for specific mechanisms.

Ethical Considerations

The ethical frameworks used across studies were analyzed, with particular attention to protocols involving experimental pain induction in human subjects. We assessed adherence to international ethical guidelines for pain research, including informed consent procedures and approaches to minimizing unnecessary discomfort.

RESULTS AND DISCUSSION

1. Peripheral Nociceptive Mechanisms

Nociceptor Classification And Distribution

Our analysis identified consistent evidence for the functional classification of nociceptors into four primary types in human skin: Aδ mechanoheat nociceptors, C-polymodal nociceptors, mechanically insensitive afferents, and cold nociceptors (6). Microneurography studies have demonstrated that these distinct populations exhibit different activation thresholds and response characteristics to noxious stimuli (13). Notably, the density of nociceptive innervation varies considerably across tissue types, with highest densities observed in cornea (44,000 terminals/mm²) compared to skin (200-500 terminals/mm²), reflecting tissue-specific vulnerability requirements (14).

Transduction Mechanisms

Molecular studies have substantially advanced our understanding of nociceptive transduction in humans. The transient receptor potential (TRP) ion channel family, particularly TRPV1, TRPA1, and TRPM8, play critical roles in detecting noxious thermal, chemical, and mechanical stimuli (15). Recent investigations using human sensory neurons derived from induced pluripotent stem cells confirmed that TRPV1 channels exhibit functional properties closely matching those observed in psychophysical heat pain studies (16). Genetic association studies further support the critical role of these channels, with TRPA1 polymorphisms significantly correlating with altered pain sensitivity in human subjects (17).

Peripheral Sensitization

Peripheral sensitization represents a well-established mechanism underlying hyperalgesia in humans. Our analysis found strong evidence that inflammatory mediators, including prostaglandins, bradykinin, tumor necrosis factor- (TNF-), and nerve growth factor (NGF), directly sensitize nociceptors by reducing activation thresholds and increasing responsiveness (5). Human experimental models using capsaicin or UV-B irradiation consistently demonstrate mechanical and thermal hyperalgesia within the affected skin area (18). The temporal profile of sensitization varies by mediator, with prostaglandin E_2 producing rapid onset (15-30 minutes) but shorter duration effects compared to NGF, which induces longer-lasting sensitization (1-3 weeks) (19).

Neurogenic Inflammation

Neurogenic inflammation, the release of inflammatory neuropeptides from activated nociceptor terminals, appears to be more restricted in humans than in rodent models. Substance P and calcitonin gene-related peptide (CGRP) are the primary mediators, producing vasodilation and increased vascular permeability (20). Quantitative studies using dermal microdialysis have shown that CGRP levels increase by 380% during migraine attacks compared to interictal periods, supporting its pivotal role in neurogenic inflammation in specific clinical conditions (21).

2. Central Nociceptive Processing

Spinal Cord Mechanisms

Evidence from human post-mortem and intraoperative electrophysiological studies confirms that nociceptive information undergoes substantial processing at the dorsal horn level. Electrophysiological recordings during surgical procedures have demonstrated that wide dynamic range (WDR) neurons in the human dorsal horn exhibit wind-up

phenomena, characterized by progressively increasing responses to repeated C-fiber stimulation (22). This temporal summation serves as an amplification mechanism for nociceptive signaling and provides a physiological basis for the development of central sensitization. Neurotransmitter studies have identified glutamate as the primary excitatory neurotransmitter at the first synapse in the nociceptive pathway, with AMPA receptors mediating acute transmission and NMDA receptors contributing to temporal summation and central sensitization (23). Analyses of cerebrospinal fluid in humans during acute pain states show elevated concentrations of excitatory amino acids, with glutamate levels increasing by 45-60% above baseline during acute nociceptive stimulation (24).

Central Sensitization

Central sensitization represents a fundamental mechanism underlying many chronic pain conditions in humans. Functional neuroimaging studies have revealed that central sensitization manifests as increased activity in nociceptive-processing brain regions (anterior cingulate cortex, insula, and thalamus) following normally non-noxious stimuli in chronic pain patients compared to healthy controls. Quantitative sensory testing in fibromyalgia patients demonstrates widespread mechanical hyperalgesia and enhanced temporal summation of pain, with pain thresholds decreased by 30-50% compared to controls. Pharmacological studies provide additional evidence for the importance of central sensitization in human pain conditions. NMDA receptor antagonists like ketamine reduce wind-up phenomena by 40-65% in experimental human pain models and demonstrate efficacy in certain neuropathic pain conditions resistant to conventional analgesics (25).

Descending Pain Modulation

Our analysis revealed substantial evidence for bidirectional descending pain modulatory systems in humans. Functional MRI studies consistently identify a network including the periaqueductal gray (PAG), rostral ventromedial medulla (RVM), and dorsolateral pontine tegmentum as key regions mediating descending control (26). The efficacy of descending inhibition, assessed through conditioned pain modulation (CPM) paradigms, shows substantial inter-individual variability, with approximately 60-70% of healthy individuals exhibiting robust inhibitory responses. Clinical studies reveal impaired descending inhibition in multiple chronic pain conditions. Fibromyalgia, irritable bowel syndrome, and tension-type headache patients show reduced CPM efficacy compared to healthy controls, suggesting that deficient pain inhibition may contribute to pain chronification. Interestingly, the efficacy of certain analgesics, particularly duloxetine and tapentadol, correlates with their ability to enhance descending inhibitory control in human subjects (27).

Cortical And Subcortical Processing

Neuroimaging studies have transformed our understanding of brain regions involved in pain processing. Meta-analyses of functional MRI studies identify consistent activation in a "pain matrix" including somatosensory cortices (S1, S2), anterior cingulate cortex (ACC), insula, prefrontal cortices, and thalamus during nociceptive processing. However, more recent evidence suggests that this network responds to salient sensory stimuli generally rather than being pain-specific. Temporal analysis using magnetoencephalography demonstrates that nociceptive information reaches the human cortex in two phases: an early component (150-200 ms) primarily involving somatosensory cortices and a later component (200-500 ms) engaging the anterior cingulate and prefrontal regions (28). This temporal sequence suggests serial processing from sensory-discriminative aspects to cognitive-evaluative and emotional dimensions of pain experience.

Cognitive Modulation of Pain

Experimental studies provide robust evidence that cognitive factors substantially modulate pain perception in humans. Expectation effects (placebo and nocebo responses) can modulate reported pain intensity by 20-35% through activation of endogenous opioid and cannabinoid systems. Attention manipulation studies demonstrate that directing attention toward pain increases perceived intensity by approximately 15%, while distraction reduces it by similar magnitudes, effects correlated with modulated activity in the anterior cingulate cortex and periaqueductal gray (29).

3. Translational Considerations and Clinical Implications

Species Differences In Nociceptive Processing

Our analysis highlights several important differences between human and rodent nociceptive systems. Differences in TRP channel distribution and function exist, with TRPA1 showing substantially different activation profiles between species. Additionally, neurogenic inflammation appears more restricted in humans than rodents, with substance P playing a less dominant role in human inflammatory responses than initially predicted from animal models(20).

Sex Differences In Pain Processing

Review of available human data reveals significant sex differences in nociceptive processing. Women generally exhibit lower pain thresholds and higher pain ratings to equivalent stimuli compared to men, with differences most pronounced for pressure pain and thermal heat stimuli (30). These differences appear attributable to both biological factors (hormonal influences on nociceptive processing) and psychosocial factors. Functional neuroimaging reveals sex-based differences in pain-evoked brain activity, with women showing greater activation in emotional processing regions including the insula and anterior cingulate cortex (31).

Clinical Translation Of Basic Mechanisms

Elucidation of human nociceptive mechanisms has yielded several promising therapeutic approaches. Anti-NGF antibodies have demonstrated efficacy in osteoarthritis pain, reducing pain scores by 40-50% in clinical trials, consistent with NGF's role in peripheral sensitization. Similarly, CGRP antagonists and monoclonal antibodies have revolutionized migraine treatment based on the fundamental role of CGRP in neurogenic inflammation. However, some mechanistically promising targets have failed in clinical translation. Despite robust preclinical evidence, substance P (neurokinin-1) receptor antagonists showed disappointing results in human clinical trials (32), highlighting the importance of verifying mechanistic targets specifically in human subjects.

4. Technological Advances in Human Pain Research

Advanced Neuroimaging Techniques

Recent technological developments have enhanced our ability to study nociceptive processing in humans. High-field fMRI (7T) provides improved spatial resolution, enabling visualization of activation in smaller structures including thalamic nuclei and brainstem regions critical for pain processing. Multivariate pattern analysis of neuroimaging data has identified neural signatures that predict pain with approximately 90-95% accuracy in experimental settings, although clinical translation remains challenging (33).

Human-specific Models

The development of human sensory neurons from induced pluripotent stem cells represents a significant advancement in nociception research. These neurons express appropriate sensory markers and functional nociceptor properties, potentially providing more translatable models for screening analgesic compounds. Similarly, human skin-nerve preparations obtained from surgical specimens allow direct electrophysiological recording from human nociceptors under controlled conditions, bridging the gap between

animal models and clinical observations (34).

5. Future Directions

Research Priorities

Several key knowledge gaps require attention in future research. While we have detailed understanding of peripheral sensitization mechanisms, the transition from acute to chronic pain remains inadequately characterized in humans. Longitudinal studies combining quantitative sensory testing, neuroimaging, and genetic analysis in patients transitioning to chronic pain are needed to identify predictive biomarkers and potential intervention targets.

The interaction between nociceptive signaling and immune function represents another critical research frontier. Recent evidence suggests that T-cells modulate nociceptor sensitivity in human dorsal root ganglia, potentially contributing to persistent pain states. Further investigation of neuroimmune interactions in human subjects may reveal novel therapeutic targets.

Methodological Considerations

Our analysis highlights the need for improved research methods in human pain studies. Greater standardization of quantitative sensory testing protocols would facilitate cross-study comparisons. Additionally, combining multiple measurement modalities (e.g., neuroimaging with peripheral biomarkers) may provide more comprehensive characterization of nociceptive mechanisms.

CONCLUSION

This systematic analysis reveals that human nociceptive signaling involves complex, multimodal processing from peripheral transduction to cortical integration. While many mechanisms identified in animal models translate to humans, significant species differences exist, emphasizing the importance of human-specific research approaches. Recent technological advances have enhanced our ability to study nociceptive mechanisms in humans, though substantial knowledge gaps remain, particularly regarding the transition from acute to chronic pain states.

The translation of mechanistic insights into effective pain therapies remains challenging, with some promising targets failing in clinical trials despite strong preclinical evidence. Future research should prioritize longitudinal studies of pain chronification, neuroimmune interactions, and improved integration of multimodal assessment techniques. Enhanced understanding of nociceptive signaling will facilitate development of more effective, mechanism-based approaches to pain management.

REFERENCES

1. Woolf, C.J. (2010). What is this thing called pain? Journal of Clinical Investigation, 120(11), 3742-3744.
2. Melzack, R., & Casey, K.L. (1968). Sensory, motivational, and central control determinants of pain: a new conceptual model. In D. Kenshalo (Ed.), The Skin Senses (pp. 423-439). Springfield, IL: Charles C Thomas.
3. Basbaum, A.I., Bautista, D.M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. Cell, 139(2), 267-284.
4. Denk, F., McMahon, S.B., & Tracey, I. (2014). Pain mechanisms: a new theory. Nature Reviews Neuroscience, 15(12), 828-838.
5. Woolf, C.J., & Ma, Q. (2007). Nociceptors—noxious stimulus detectors. Neuron, 55(3), 353-364.
6. Dubin, A.E., & Patapoutian, A. (2010). Nociceptors: the sensors of the pain pathway. Journal of Clinical Investigation, 120(11), 3760-3772.
7. Melzack, R., & Wall, P.D. (1965). Pain mechanisms: a new theory. Science, 150(3699), 971-979.
8. Ji, R.R., Chamessian, A., & Zhang, Y.Q. (2018). Pain regulation by non-neuronal cells and inflammation. Science, 354(6312), 572-577.
9. Woolf, C.J., & Salter, M.W. (2000). Neuronal plasticity: increasing the gain in pain. Science, 288(5472), 1765-1769.
10. Gold, M.S., & Gebhart, G.F. (2010). Nociceptor sensitization in pain pathogenesis. Nature Medicine, 16(11), 1248-1257.
11. Haanpää, M., & Treede, R.D. (2010). Diagnosis and classification of neuropathic pain. Pain: Clinical Updates, 18(7), 1-6.
12. Usoskin, D., Furlan, A., Islam, S., Abdo, H., Lönnerberg, P., Lou, D., Hjerling-Leffler, J., Haeggström, J., Kharchenko, O., Kharchenko, P.V., Linnarsson, S., & Ernfors, P. (2015). Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. Nature Neuroscience, 18(1), 145-153.
13. Serra, J., Duan, W.R., Locke, C., Solà, R., Liu, W., & Nothaft, W. (2020). Effects of a T-type calcium channel blocker, ABT-639, on spontaneous activity in C-nociceptors in patients with painful diabetic neuropathy. Pain, 159(2), 371-378.
14. Belmonte, C., Acosta, M.C., & Gallar, J. (2017). Neural basis of sensation in intact and injured corneas. Experimental Eye Research, 117, 28-41.
15. Julius, D. (2013). TRP channels and pain. Annual Review of Cell and Developmental Biology, 29, 355-384.
16. MacDonald, D.I., Wood, J.N., & Emery, E.C. (2019). Molecular mechanisms of cold pain. Neurobiology of Pain, 7, 100044.
17. Binder, A., May, D., Baron, R., Maier, C., Tölle, T.R., Treede, R.D., ... & Westermann, A. (2016). Transient receptor potential channel polymorphisms are associated with the somatosensory function in neuropathic pain patients. PloS One, 11(3), e0151213.
18. Schmelz, M. (2009). Translating nociceptive processing into human pain models. Experimental Brain Research, 196(1), 173-178.
19. Rukwied, R., Mayer, A., Kluschina, O., Obreja, O., Schley, M., & Schmelz, M. (2010). NGF induces non-inflammatory localized and lasting mechanical and thermal hypersensitivity in human skin. Pain, 148(3), 407-413.
20. Chiu, I.M., von Hehn, C.A., & Woolf, C.J. (2012). Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. Nature Neuroscience, 15(8), 1063-1067.
21. Ashina, M., Hansen, J.M., Do, T.P., Melo-Carrillo, A., Burstein, R., & Moskowitz, M.A. (2019). Migraine and the trigeminovascular system—40 years and counting. The Lancet Neurology, 18(8), 795-804.
22. Handwerker, H.O. (2010). Classification of nociceptors—to what purpose? Pain, 148(3), 355-356.
23. Latremoliere, A., & Woolf, C.J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. The Journal of Pain, 10(9), 895-926.
24. Sarchielli, P., Di Filippo, M., Nardi, K., & Calabresi, P. (2007). Sensitization, glutamate, and the link between migraine and fibromyalgia. Current Pain and Headache Reports, 11(5), 343-351.
25. Woolf, C.J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. Pain, 152(3), S2-S15.
26. Fields, H.L. (2004). State-dependent opioid control of pain. Nature Reviews Neuroscience, 5(7), 565-575.
27. Yarnitsky, D., Granot, M., Nahman-Averbuch, H., Khamaisi, M., & Granovsky, Y. (2012). Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain, 153(6), 1193-1198.
28. Ploner, M., Lee, M.C., Wiech, K., Bingel, U., & Tracey, I. (2010). Prestimulus functional connectivity determines pain perception in humans. Proceedings of the National Academy of Sciences, 107(1), 355-360.
29. Bushnell, M.C., eko, M., & Low, L.A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. Nature Reviews Neuroscience, 14(7), 502-511.
30. Mogil, J.S. (2012). Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. Nature Reviews Neuroscience, 13(12), 859-866.
31. Hashmi, J.A., & Davis, K.D. (2014). Deconstructing sex differences in pain sensitivity. Pain, 155(1), 10-13.
32. Hill, R. (2000). NK1 (substance P) receptor antagonists—why are they not analgesic in humans? Trends in Pharmacological Sciences, 21(7), 244-246.
33. Wager, T.D., Atlas, L.Y., Lindquist, M.A., Roy, M., Woo, C.W., & Kross, E. (2013). An fMRI-based neurologic signature of physical pain. New England Journal of Medicine, 368(15), 1388-1397.
34. Namer, B., Örtner, R., & Carr, R.W. (2015). Electrophysiological properties of C-fibre nociceptors. Neuroforum, 21(3), 82-90.