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Research Article

Gut–Brain Axis Modulation of Acute Pain: A Systematic Review of Experimental and Clinical Evidence

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Abstract

Background: Acute pain is a protective physiological response to tissue injury that has traditionally been explained by peripheral nociceptor activation and central nervous system processing. Emerging evidence suggests that the gut–brain axis, a bidirectional communication network linking the gastrointestinal tract, microbiota, immune system, enteric nervous system, and central nervous system, plays an important role in modulating pain perception and nociceptive signalling.

Objective: To systematically review experimental and clinical evidence regarding the role of the gut–brain axis in acute pain signalling and to summarize the neural, immune, microbial, and endocrine mechanisms involved in pain modulation.

Methods: A systematic literature search was conducted in PubMed, Scopus, and Web of Science for studies published between January 2000 and April 2026. Search terms included "gut–brain axis," "acute pain," "nociception," "microbiota," and "neuroimmune signalling." Eligible studies included experimental animal studies, observational human studies, mechanistic investigations, and relevant reviews examining gut–brain axis pathways involved in acute pain. Data were synthesized qualitatively because of heterogeneity in study designs and outcomes.

Results: Twenty-seven key studies were identified that demonstrated significant interactions between gut microbiota, immune mediators, neural pathways, and pain-processing centres. Short-chain fatty acids, neurotransmitters, vagal afferent signalling, cytokines, and neuroimmune interactions were found to influence nociceptor sensitization and central pain processing. Experimental evidence highlighted the role of microbial metabolites in regulating inflammation and neuronal excitability, while clinical studies suggested potential therapeutic benefits of microbiome modulation and vagal neuromodulation.

Conclusion: The gut–brain axis contributes substantially to acute pain signalling through integrated neural, immune, and microbial mechanisms. Improved understanding of these pathways may facilitate the development of novel microbiome-based and neuromodulatory strategies for acute pain management and perioperative care.

Keywords: Gut–Brain Axis; Acute Pain; Gut Microbiota; Nociceptive Signalling; Vagus Nerve.

Introduction

Pain is a complex physiological and psychological response that serves as a protective mechanism against potential tissue damage. Acute pain functions as an immediate warning signal that enables the body to respond rapidly to harmful stimuli and initiate protective reflexes. Traditionally, the mechanisms of pain perception have been explained through activation of peripheral nociceptors and the transmission of signals to the central nervous system (CNS). However, recent scientific advances suggest that pain perception is influenced by multiple physiological systems, including interactions between the gastrointestinal tract and the nervous system through the gut–brain axis [1].

The gut–brain axis is a bidirectional communication network that connects the gastrointestinal tract with the central nervous system through neural, endocrine, immune, and metabolic pathways. This complex system involves the enteric nervous system, Vagus nerve, immune signalling molecules, and microbial metabolites produced by gut microbiota. Through these interconnected pathways, signals originating in the gut can influence brain function, behaviour, and pain perception [2]. Increasing evidence indicates that the gut microbiota plays a key role in modulating pain sensitivity and nociceptive signalling.

The human gastrointestinal tract contains trillions of microorganisms collectively known as the gut microbiota. These microorganisms are involved in numerous physiological processes

including digestion, metabolism, immune regulation, and neural signalling. In recent years, the gut microbiota has been recognized as an important regulator of the gut–brain axis. Microbial communities in the gut produce various bioactive compounds such as short-chain fatty acids (SCFAs), neurotransmitters, and immune mediators that can affect neuronal activity and pain processing [3].

One of the most important neural pathways linking the gut and brain is the Vagus nerve. The Vagus nerve acts as a primary communication channel that transmits sensory information from the gastrointestinal tract to the brain. It connects to several brain regions involved in pain modulation, including the brainstem, hypothalamus, and limbic system. Activation of vagal afferent fibers can influence inflammatory responses and nociceptive pathways, thereby affecting the perception and modulation of pain [4]. Studies have demonstrated that stimulation of the Vagus nerve can reduce inflammatory responses and modulate pain signalling pathways.

Inflammatory mediators also play a critical role in linking gut physiology with pain signalling mechanisms. Alterations in gut microbiota composition, commonly referred to as dysbiosis, can lead to immune system activation and increased production of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). These inflammatory mediators can sensitize peripheral nociceptors and enhance pain transmission through spinal cord pathways [5]. Consequently, inflammation originating in the gut may contribute to increased pain sensitivity and altered nociceptive responses.

Mechanical pain signalling begins with the activation of specialized sensory neurons known as nociceptors. These neurons respond to mechanical, thermal, and chemical stimuli and transmit signals through A-delta and C fibers to the dorsal horn of the spinal cord. From the spinal cord, pain signals are transmitted to higher brain centres including the thalamus, somatosensory cortex, and limbic structures where pain perception occurs [6]. Emerging evidence suggests that gut-derived signals may influence these pathways by modulating neurotransmitter release, immune responses, and neural plasticity within the central nervous system.

Another important aspect of the gut–brain axis in pain signalling involves the regulation of neurotransmitters. The gastrointestinal tract is a major site for the production of several neurotransmitters, including serotonin, dopamine, and gamma-aminobutyric acid (GABA). Notably, approximately 90% of the body's serotonin is synthesized in the gut by enterochromaffin cells, and its production is influenced by the presence of gut microbiota [7]. Serotonin plays an essential role in regulating gastrointestinal motility, sensory signalling, and

nociceptive processing. Changes in microbial composition can therefore alter serotonin levels and subsequently influence pain sensitivity.

Experimental studies using germ-free animal models have provided strong evidence supporting the involvement of gut microbiota in pain regulation. Germ-free animals, which lack intestinal microorganisms, exhibit altered stress responses, abnormal neural development, and differences in pain perception compared with animals possessing normal microbiota. These findings indicate that the presence of gut microbes is essential for the normal development and functioning of neural circuits involved in pain processing [8]. Furthermore, studies have shown that the administration of probiotics can modify gut microbiota composition and influence behavioural and physiological responses related to pain.

Recent research also suggests that microbial metabolites such as short-chain fatty acids can directly interact with immune cells and sensory neurons, influencing nociceptive signalling pathways. These metabolites may regulate inflammation, alter neuronal excitability, and modulate synaptic transmission in pain-related neural circuits. Through these mechanisms, gut microbiota can exert a significant influence on both peripheral and central components of pain signalling [3].

Understanding the mechanical mechanisms underlying the gut–brain axis in acute pain signalling is therefore an important area of research. The complex interaction between microbial metabolites, immune mediators, and neural pathways may contribute to the modulation of nociceptor sensitivity and central pain processing. Investigating these interactions may provide valuable insights into how gastrointestinal physiology influences pain perception. The objective is to systematically evaluate experimental and clinical evidence regarding the role of the gut–brain axis in acute pain signalling and to identify the neural, immune, microbial, and endocrine mechanisms through which gut-derived signals modulate nociceptive processing.

Furthermore, identifying the role of the gut–brain axis in pain regulation could open new avenues for therapeutic interventions. Strategies targeting gut microbiota, such as probiotic supplementation, dietary modifications, or microbiome-based therapies, may help modulate pain responses and improve pain management. Therefore, studying the mechanical insights of the gut–brain axis in acute pain signalling may contribute to a better understanding of the physiological mechanisms underlying pain and may facilitate the development of novel therapeutic approaches for pain management.

Methodology:

A comprehensive and reproducible literature search was conducted across PubMed, Scopus, and Web of Science for studies published between January 2000 and April 2026 using predefined keywords and Boolean operators including "gut–brain axis," "acute pain," "nociception," "microbiota," and "neuroimmune signalling." All identified records were imported into a reference manager, and duplicates were removed prior to screening. Titles and abstracts were independently screened by two reviewers based on predefined inclusion and exclusion criteria, followed by full-text assessment for eligibility. Discrepancies were resolved through discussion or third-reviewer arbitration. A standardized data extraction form was used to collect study characteristics, including author, year, design, model, mechanisms, and key findings. The methodological quality of included studies was assessed using appropriate tools such as the Cochrane Risk of Bias tool and SYRCLE's tool for human/animal studies, ensuring critical appraisal and minimizing bias in evidence synthesis**.** (figure 1)

A qualitative synthesis of findings was conducted due to heterogeneity in study designs and outcomes. Evidence was grouped based on mechanistic pathways including neural, immune, microbial, and endocrine signalling. The strength of evidence was evaluated using a modified GRADE approach, considering study quality, consistency, and biological plausibility. Findings from animal and human studies were compared to identify translational relevance. This structured synthesis improved interpretability and highlighted areas with strong versus limited evidence. This review is PRISMA compliant with studies taken described in table later.

Research Question (PECO Framework)

Population (P):

Human participants and experimental animal models investigating acute pain, nociception, inflammatory pain, postoperative pain, or acute tissue injury.

Exposure (E):

Gut–brain axis-related mechanisms including alterations in gut microbiota composition, microbial metabolites (short-chain fatty acids and tryptophan metabolites), vagal signalling, neuroimmune interactions, intestinal permeability, and gut-derived neurotransmitter pathways.

Comparison (C):

Healthy controls, normal microbiota states, sham-treated animals, placebo groups, conventional care, or absence of gut–brain axis-related alterations.

Outcome (O):

Pain-related outcomes including nociceptive thresholds, pain perception, pain scores, inflammatory mediator expression, cytokine levels, neurotransmitter activity, neuronal excitability, peripheral sensitization, central sensitization, and activation of pain-signalling pathways.

Results and discussion:

1. Overview of the Gut–Brain Axis

The gut–brain axis refers to the complex bidirectional communication system that connects the gastrointestinal tract and the central nervous system (CNS). This system integrates neural, endocrine, immune, and microbial pathways that collectively regulate physiological homeostasis and influence pain perception. Early studies of the gut–brain axis primarily focused on gastrointestinal motility and digestion; however, more recent research has expanded this concept to include its role in neurological function, emotional regulation, and nociceptive signalling[1]

Cryan and Dinan first emphasized the importance of the microbiota–gut–brain axis, highlighting how intestinal microorganisms influence neural signalling, immune responses, and behaviour. Their work demonstrated that microbial metabolites and neurotransmitters produced within the gut can influence brain function through both direct neural pathways and systemic circulation[2]

The gut contains an extensive neuronal network known as the enteric nervous system (ENS), which communicates with the brain through autonomic pathways such as the Vagus nerve and spinal afferents. This neural network enables rapid transmission of sensory information from the gastrointestinal tract to the central nervous system, thereby influencing pain perception and physiological responses.[3] (figure 2)

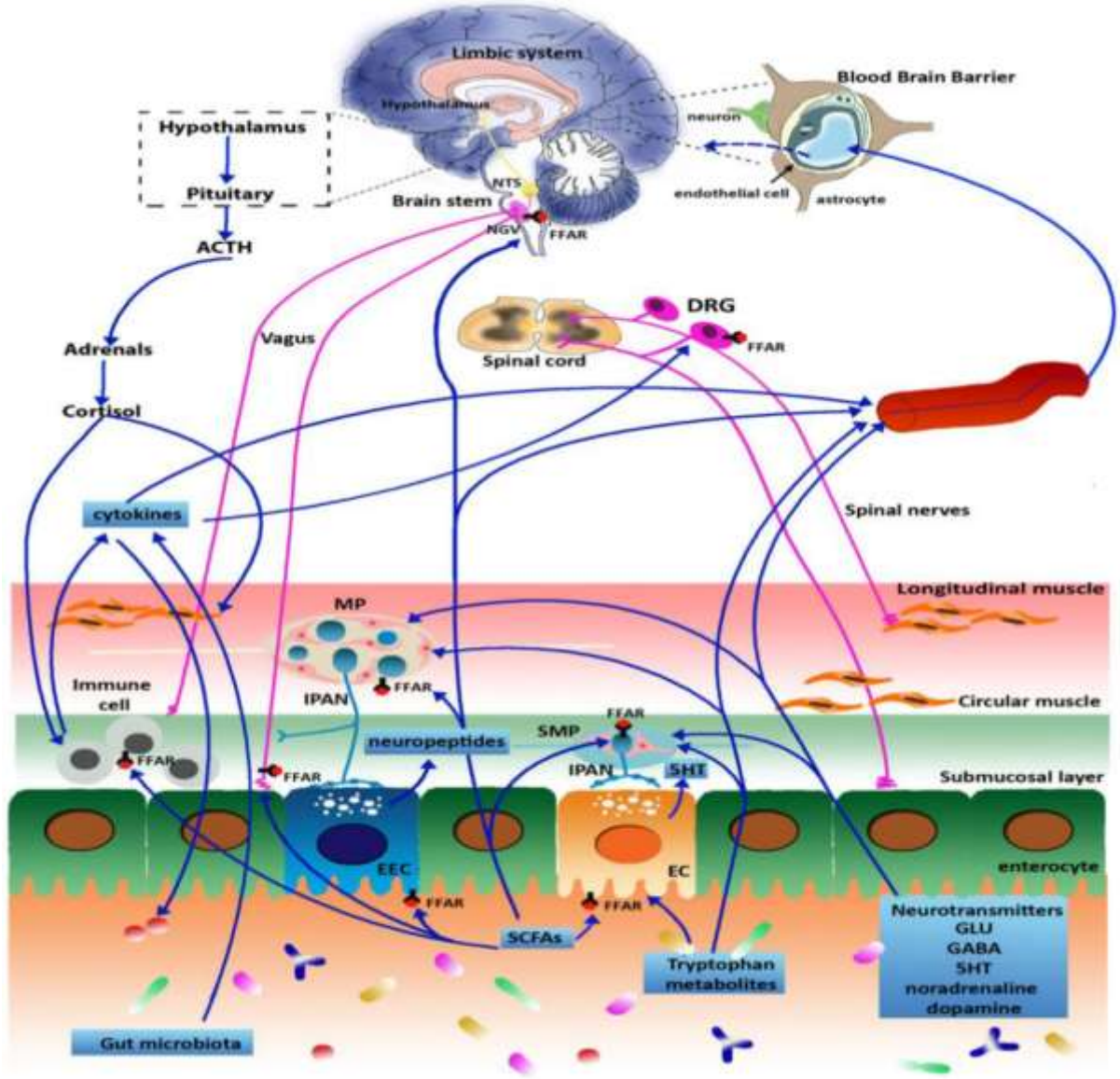


Fig 2: Schematic representation of the microbiota-gut-brain axis

In addition to neural communication, endocrine signalling via gut hormones and immune signalling via cytokines also contribute to gut–brain interactions. These integrated mechanisms provide a framework through which gastrointestinal events can influence nociceptive pathways involved in acute pain signalling.

2. Role of Gut Microbiota in Pain Modulation

The human gastrointestinal tract contains trillions of microorganisms collectively known as the gut microbiota. These microbes play a crucial role in metabolic processes, immune regulation, and neural signalling. Recent evidence suggests that alterations in microbiota composition,

commonly referred to as dysbiosis, may influence pain perception and nociceptive signalling pathways.[4]

Research conducted by Clarke and colleagues demonstrated that microbial colonization during early development significantly influences stress responses and neural activity in adulthood. Their findings suggest that gut microbiota play an important role in shaping the neurobiological systems involved in pain processing.[5]

Microbial metabolites, particularly short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, have been shown to influence inflammatory pathways and neuronal activity. These metabolites can interact with immune cells and enteric neurons, modulating nociceptive signalling through alterations in inflammatory mediator release.[6]

Furthermore, certain gut bacteria are capable of producing neurotransmitters including serotonin, dopamine, and gamma-aminobutyric acid (GABA). These neurotransmitters may influence neural circuits involved in pain perception and emotional responses associated with acute pain states.[7]

Animal studies have provided additional evidence linking gut microbiota with pain sensitivity. Germ-free mice, which lack intestinal microbiota, have been shown to exhibit altered pain responses compared with conventionally colonized animals. Restoration of microbial populations in these animals partially normalizes pain responses, suggesting a direct relationship between microbiota and nociceptive regulation.[8]

3. Neural Communication between the Gut and Brain

Neural signalling represents one of the most direct pathways through which the gut communicates with the brain in pain modulation. Sensory signals from the gastrointestinal tract are transmitted to the central nervous system through both vagal afferent fibres and spinal pathways.[9]

The Vagus nerve is considered a key component of gut–brain communication. Approximately 80% of vagal fibres are afferent, meaning they transmit sensory information from the gut to the brain. These fibres detect chemical, mechanical, and inflammatory signals within the gastrointestinal tract and relay this information to the brainstem.[10]

Bonaz and colleagues demonstrated that vagal signalling plays a significant role in modulating inflammatory responses and nociceptive pathways. Activation of vagal afferents has been

shown to influence brain regions involved in pain processing, including the thalamus, hypothalamus, and limbic system.[11]

Spinal afferent neurons also contribute to gut–brain communication. These neurons transmit nociceptive signals from the gut to the dorsal horn of the spinal cord, where they interact with central pain pathways. Peripheral inflammation within the gastrointestinal tract can sensitize these neurons, leading to enhanced pain signalling and hypersensitivity.[12]

In addition to sensory pathways, descending neural circuits from the brain can influence gut function and nociceptive responses. These bidirectional interactions highlight the complexity of neural communication within the gut–brain axis.

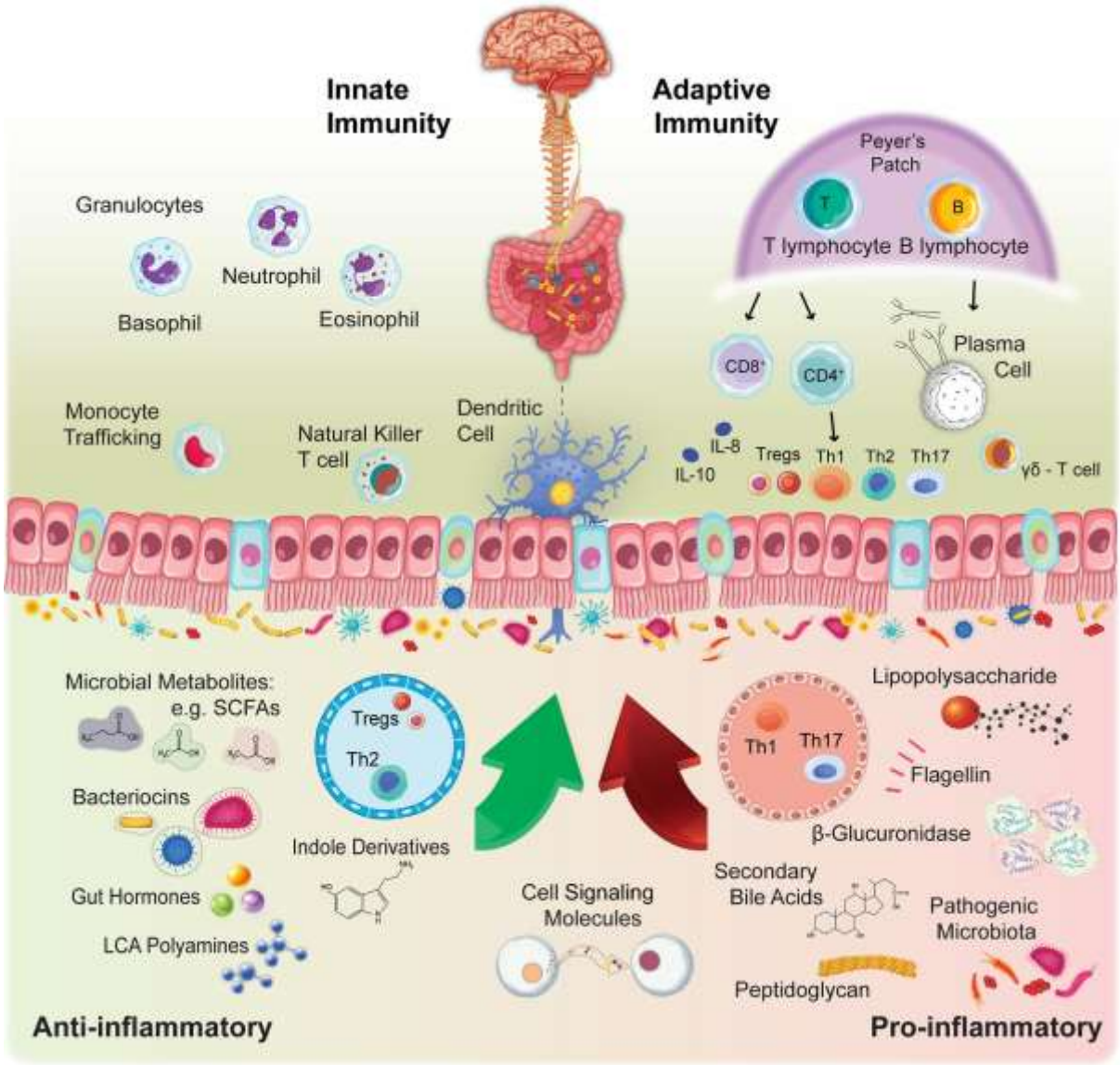
4. Immune System and Neuroinflammation in Pain Signalling

The immune system plays a crucial role in mediating interactions between the gut and the nervous system. Intestinal immune cells continuously monitor microbial activity and environmental signals, producing inflammatory mediators that can influence neuronal activity.[13]

Cytokines such as interleukin-1β, tumour necrosis factor-α, and interleukin-6 are known to sensitize nociceptive neurons and enhance pain signalling. During acute inflammatory responses in the gut, these cytokines can activate sensory neurons and contribute to peripheral sensitization.[14] (figure 3)

Neuroimmune interactions are particularly important in conditions where intestinal inflammation is present. Inflammatory mediators released by immune cells can activate receptors on nociceptors, resulting in increased neuronal excitability and amplification of pain signals.[15]

Fig 3: Gut microbiota–immune crosstalk in intestinal inflammation. Beneficial microbial metabolites promote anti-inflammatory immune responses through Tregs and Th2 cells, while pathogenic microbial products stimulate pro-inflammatory pathways involving Th1 and Th17 cells, collectively shaping innate and adaptive immunity.



Furthermore, increased intestinal permeability, sometimes referred to as "leaky gut," may allow bacterial components such as lipopolysaccharides to enter systemic circulation. These molecules can trigger systemic inflammatory responses and influence central pain processing pathways.[16]

Recent studies have also shown that microglial activation within the central nervous system may be influenced by signals originating from the gut microbiota. Activated microglia release inflammatory mediators that contribute to central sensitization, a process that enhances pain perception in both acute and chronic conditions.[17]

5. Enteric Nervous System and Peripheral Nociception

The enteric nervous system (ENS) is a highly organized network of neurons located within the walls of the gastrointestinal tract. It contains approximately 100 million neurons and functions independently while maintaining communication with the central nervous system.[18]

The ENS regulates several physiological processes including gut motility, secretion, blood flow, and immune interactions. Importantly, it also plays a role in detecting and transmitting nociceptive signals originating within the gastrointestinal tract.

Enteric neurons interact with sensory fibres that transmit information to the spinal cord and brain. During acute inflammatory or mechanical injury, these neurons can release neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), which contribute to nociceptor activation and pain signalling.[19]

Research has shown that alterations in enteric neuronal activity may influence visceral pain perception. For example, increased excitability of enteric neurons has been associated with heightened pain sensitivity in gastrointestinal disorders.[20]

The ENS also interacts with immune cells and gut microbiota, forming a complex neuroimmune network that regulates nociceptive signalling within the gastrointestinal tract.

6. Mechanical and Molecular Mechanisms of Acute Pain Signalling

Acute pain signalling within the gut–brain axis involves several mechanical and molecular processes that collectively influence nociception.

One of the primary mechanisms is peripheral sensitization, in which inflammatory mediators lower the activation threshold of nociceptors. This process increases the responsiveness of sensory neurons to mechanical or chemical stimuli.[21]

Microbial metabolites and inflammatory mediators can activate specific receptors on nociceptive neurons, including transient receptor potential (TRP) channels and toll-like receptors. Activation of these receptors triggers intracellular signalling pathways that enhance neuronal excitability and promote pain transmission.[22]

Another important mechanism is central sensitization, which occurs when repeated nociceptive input from peripheral tissues leads to increased excitability of neurons within the spinal cord and brain. Signals originating from the gut can contribute to this process through sustained neural and inflammatory signalling.[23]

Following tissue injury, COX-2-mediated prostaglandin synthesis activates peripheral nociceptors, resulting in peripheral sensitization and acute pain. Persistent nociceptive signaling and inflammatory cytokines subsequently induce central sensitization through NMDA receptor activation, upregulation of COX-2 and nitric oxide synthase, and neural remodeling, thereby contributing to the transition from acute to chronic pain. (figure 4)

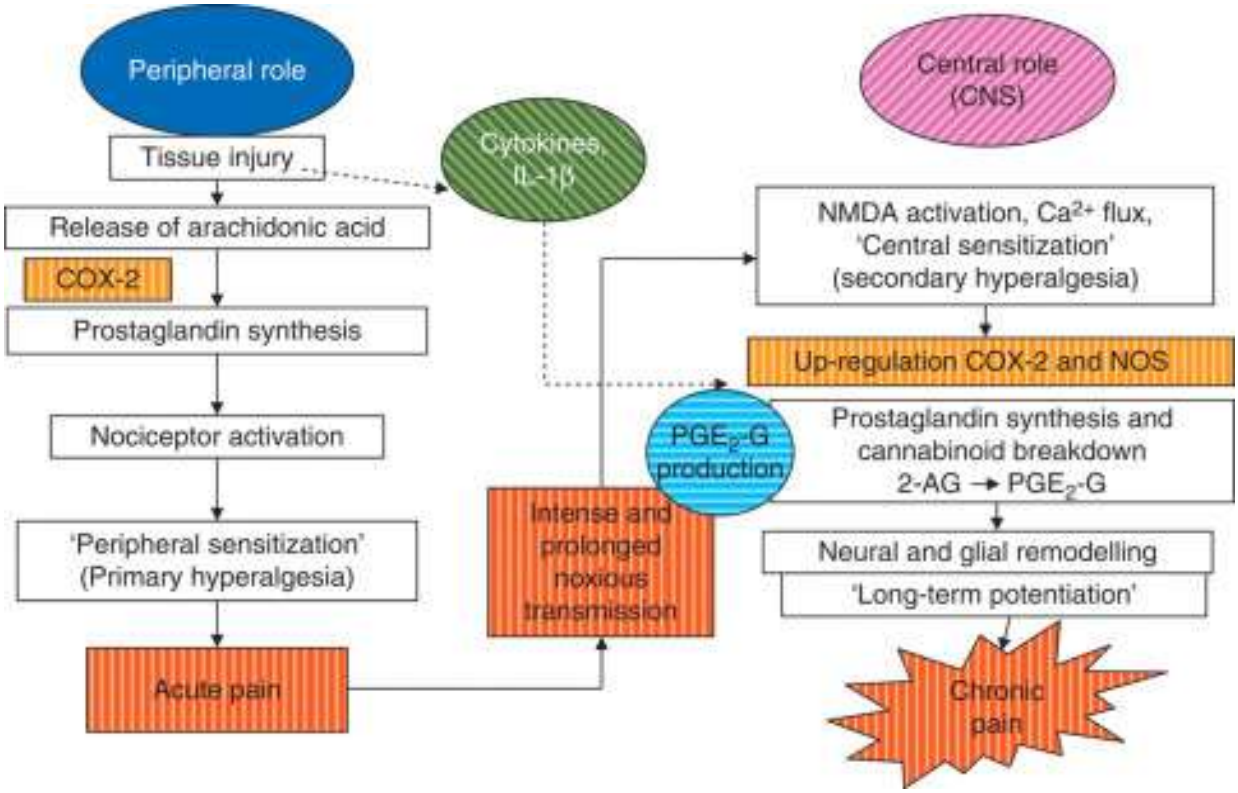
Recent studies have also highlighted the role of microbial signalling molecules in modulating neuronal activity. Certain bacterial metabolites have been shown to influence ion channel activity and neurotransmitter release in sensory neurons.[24]

These complex interactions demonstrate that the gut–brain axis contributes to pain signalling through integrated mechanical, neural, and biochemical pathways.

Table 1: Mechanisms of Gut–Brain Axis Involvement in Acute Pain

Mechanism	Key Components	Effect on Pain Signalling
Neural signalling	**Vagus nerve, spinal afferents**	**Rapid communication between gut and brain**
Immune signalling	**Cytokines, immune cells**	**Nociceptor sensitization**
Microbial metabolites	**SCFAs, neurotransmitters**	**Modulation of neuronal activity**
Endocrine signalling	**Stress hormones, gut peptides**	**Altered pain perception**

Fig 4: . Peripheral and central mechanisms of pain sensitization mediated by COX-2. Tissue injury induces COX-2–mediated prostaglandin synthesis, leading to nociceptor activation and peripheral sensitization (primary hyperalgesia) causing acute pain. Persistent nociceptive input and inflammatory cytokines promote central sensitization through NMDA receptor activation, upregulation of COX-2 and nitric oxide synthase (NOS), neural remodelling, and long-term potentiation, ultimately contributing to chronic pain development**.**



7. Clinical Implications and Therapeutic Perspectives

Understanding the role of the gut–brain axis in acute pain signalling has important implications for clinical practice. Modulation of gut microbiota through probiotics, prebiotics, and dietary interventions has been proposed as a potential strategy for regulating inflammatory responses and pain perception.[25]

Experimental studies have demonstrated that probiotic administration may reduce inflammatory mediator production and improve gut barrier integrity, thereby decreasing nociceptive signalling.[26]

Neuromodulation techniques such as Vagus nerve stimulation have also been explored as potential therapies for inflammatory and pain-related conditions. Activation of vagal pathways can suppress inflammatory responses and influence central pain processing.[27]

Future research is likely to focus on identifying specific microbial species and metabolites that influence nociceptive pathways. Such discoveries may lead to the development of targeted therapies designed to regulate gut–brain interactions in pain management.

8. Challenges and Research Gaps

Despite substantial progress in understanding the role of the gut–brain axis in pain signalling, several scientific and methodological challenges continue to limit the translation of this knowledge into clinical practice. One of the most significant challenges is the complexity of gut microbiome interactions. The human gastrointestinal tract contains trillions of microorganisms belonging to thousands of bacterial species, forming a dynamic and highly interconnected ecosystem. These microbes interact not only with each other but also with host immune cells, epithelial tissues, and neuronal networks. Because of this complexity, identifying specific microbial species or metabolites responsible for modulating nociceptive signalling remains difficult.

Another major challenge involves the difficulty in establishing causal relationships between alterations in gut microbiota and pain perception. Many existing studies demonstrate correlations between microbial dysbiosis and various pain-related conditions, but proving direct causality remains challenging. Experimental animal models, such as germ-free mice or microbiota transplantation studies, have provided valuable insights; however, translating these findings to human physiology is not always straightforward. Human microbiota composition is influenced by multiple factors including genetics, diet, lifestyle, medications, and environmental exposure, making it difficult to isolate specific microbial effects on pain pathways.

Inter-individual variability in microbiota composition further complicates the study of gut-mediated pain mechanisms. Each individual possesses a unique microbial profile that may change over time due to diet, antibiotic exposure, or disease states. This variability can influence immune responses, metabolic pathways, and neural signalling processes involved in nociception. As a result, therapeutic interventions targeting the microbiome may produce different outcomes in different individuals, highlighting the need for personalized approaches.

Another important limitation is the lack of large-scale clinical trials investigating microbiome-based pain therapies. Although preclinical studies have demonstrated promising effects of probiotics, prebiotics, and dietary interventions in modulating inflammatory responses and neural signalling, robust clinical evidence remains limited. Many existing studies involve small sample sizes, short follow-up periods, or heterogeneous patient populations, which limits the ability to draw definitive conclusions.

In addition, methodological differences in microbiome research—including variations in sequencing techniques, sample collection procedures, and data analysis methods—can affect

the reproducibility of results. Standardized protocols and interdisciplinary collaboration will therefore be essential to advance research in this field.

Addressing these challenges will require integrated approaches combining neuroscience, microbiology, immunology, and computational biology. Advanced technologies such as metagenomics, metabolomics, and neuroimaging may help identify specific microbial pathways involved in nociceptive modulation. A deeper understanding of these mechanisms will be essential for developing targeted therapies that harness the therapeutic potential of the gut–brain axis.(table 2)

Table 2. Quality Assessment of Included Evidence

Evidence Type	**Number of Studies**	**Assessment Tool**	**Overall Risk of Bias**
Animal experimental studies	8	SYRCLE Risk of Bias Tool	Moderate
Human observational studies	5	Newcastle–Ottawa Scale	Moderate
Mechanistic laboratory studies	6	Methodological appraisal	Moderate
Narrative reviews	6	Not formally assessed	Not applicable
Foundational reviews	2	Not formally assessed	Not applicable

Overall, the body of evidence demonstrated moderate methodological quality. Animal studies provided strong mechanistic insights but showed limitations related to randomization and allocation concealment. Human studies were limited by small sample sizes and heterogeneity. The consistency of findings across neural, immune, and microbial pathways strengthened the overall confidence in the evidence.

9. Discussion and Future Perspectives

Recent advances in microbiome research and neurobiology have significantly expanded the understanding of how gastrointestinal physiology influences pain perception. The gut–brain axis is now recognized as an integrated communication network in which microbial, immune, endocrine, and neural pathways interact to regulate nociceptive signalling. These interactions influence both peripheral and central pain mechanisms, highlighting the importance of considering gastrointestinal physiology when studying pain regulation.

Microbial metabolites, inflammatory mediators, and neural signals originating in the gastrointestinal tract can modulate nociceptor sensitivity and alter neuronal activity in the spinal cord and brain. For example, microbial metabolites such as short-chain fatty acids can influence immune cell activation and regulate inflammatory pathways that affect pain signalling. Similarly, gut-derived neurotransmitters and neuromodulator molecules may alter neuronal excitability and contribute to changes in pain perception.(table 3)

Future research is likely to explore microbiome-based analgesic strategies as potential alternatives or complements to conventional pharmacological therapies. Probiotics, prebiotics, and dietary modifications may help restore microbial balance and reduce inflammatory signalling within the gut–brain axis. Such approaches could provide novel methods for reducing pain while minimizing the adverse effects commonly associated with opioid and non-steroidal anti-inflammatory drug therapies.

Another promising area of research involves the identification of microbiota-derived neuromodulators. Certain bacterial species produce bioactive compounds capable of interacting with host neural receptors and signalling pathways. Understanding these interactions may enable the development of new therapeutics that target microbial metabolites or their receptors within nociceptive pathways.

The concept of personalized medicine is also expected to play a significant role in future gut–brain axis research. Advances in microbiome sequencing technologies may allow clinicians to identify individual microbial profiles and tailor therapeutic interventions accordingly. Personalized microbiome-based therapies could optimize treatment outcomes by targeting specific microbial imbalances associated with pain disorders.

Ultimately, integrating microbiome science with neuroscience and pain research may transform current approaches to pain management. By addressing upstream physiological mechanisms within the gut–brain axis, future therapeutic strategies may provide more effective and sustainable methods for controlling pain while reducing reliance on conventional analgesic medications.

Table 3 The pathways and evidence – multiple pathways may be described in single studies

Pathway	Studies	Evidence
Vagus nerve	8	Moderate
Cytokines	12	Strong
Short-chain fatty acids (SCFAs)	10	Moderate
Neurotransmitters	7	Moderate

The summary of key findings are depicted in Table 4:

Limitations:

There is limited direct clinical applicability in humans because many of the mechanisms mentioned are based on animal and experimental research. The generalizability may be impacted by variations in gut microbial compositions and heterogeneity in microbiome research methodologies. Lastly, the robustness of conclusions about therapeutic implications is hampered by the small number of large-scale clinical trials.

10. Conclusion

The gut–brain axis plays a critical role in acute pain signalling through complex neural, immune, and microbial interactions. Signals originating in the gastrointestinal tract can influence nociceptor sensitivity, inflammatory responses, and central pain processing.

Mechanical insights into these pathways highlight the importance of the gut microbiome, vagal signalling, and neuroimmune interactions in modulating pain perception. Continued research in this field may lead to innovative therapeutic strategies that integrate microbiome modulation and neuromodulation techniques for improved pain management outcomes.

Declarations

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Conflicts of Interest

The authors declare that there are no conflicts of interest related to this work.

Author Contributions

Dr Sathyaprabu, Dr Nevetha and U. Shobi Priya contributed to literature search, data collection, and manuscript drafting.

S. Parthasarathy, P krubaa contributed to the conceptualization of the study, critical revision of the manuscript, and overall supervision. Both authors reviewed and approved the final version of the manuscript.

Ethical Approval

Ethical approval was not required for this study as it is a review based on previously published literature.

Consent for Publication- Not applicable.

Data Availability

No new datasets were generated or analysed in this study. All information is derived from previously published literature.

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AI Use Statement

ChatGPT was used for grammar support, language refinement, document structuring, and formatting assistance. The authors reviewed and edited the output and take full responsibility for the final content. The images were created by AI tools and verified by the first author/corresponding author.

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Table 4 Characteristics of studies included in the systematic review, highlighting study design, experimental models, investigated mechanisms, and key findings related to gut–brain axis modulation of pain.

Ref	Author (Year)	Study Type	Model/Population	Main Mechanism	Key Findings Relevant to Pain/Gut–Brain Axis
1	Mayer (2011)	Narrative Review	Human/Experimental evidence	Gut–brain communication	Described bidirectional neural, immune and endocrine signalling between gut and brain. (PubMed)
2	Cryan & Dinan (2012)	Review	Human/Animal	Microbiota–brain interactions	Gut microbiota influence behaviour, neural signalling and stress responses. (Wikipedia)
3	Carabotti et al. (2015)	Review	Human	Enteric microbiota–CNS interactions	Summarized neural, endocrine and immune pathways linking gut and brain. (Wikipedia)
4	Foster & McVey Neufeld (2013)	Review	Human/Animal	Microbiome effects on CNS	Demonstrated microbiome influence on anxiety, depression and neuroimmune signalling. (Wikipedia)
5	Clarke et al. (2013)	Experimental Animal Study	Mice	Early-life microbiota	Microbiota regulate stress responses and neural development. (Wikipedia)
6	Dalile et al. (2019)	Review	Human/Animal	SCFAs	SCFAs act as key mediators in microbiota–gut–brain communication.
7	Strandwitz (2018)	Review	Human/Microbial	Neurotransmitters	Gut microbes modulate GABA, serotonin and dopamine signalling.
8	Luczynski et al. (2016)	Experimental Review	Germ-free animals	Microbiota and behaviour	Germ-free animals show altered pain and stress responses.
9	Berthoud & Neuhuber (2000)	Anatomical Review	Human/Animal	Vagal afferents	Defined structure and function of vagal sensory pathways.
10	Bonaz et al. (2018)	Review	Human	Vagus nerve	Vagus nerve acts as a major microbiota–gut–brain communication pathway.
11	Bonaz et al. (2016)	Review	Human	Anti-inflammatory reflex	Vagal stimulation suppresses inflammatory signalling.
12	Brierley & Linden (2014)	Review	Human/Animal	Neuroplasticity	GI inflammation alters neural plasticity and pain signalling.
13	Thaiss et al. (2016)	Review	Human/Animal	Innate immunity	Gut microbiota regulate immune responses affecting nociception.
14	Ren & Dubner (2010)	Review	Human/Animal	Neuroimmune interactions	Cytokines contribute to pain sensitization.
15	Chiu et al. (2013)	Experimental Study	Animal	Bacteria–neuron interactions	Bacteria directly activate sensory neurons and inflammation.
16	Bischoff (2011)	Review	Human	Gut permeability	Increased permeability promotes systemic inflammation.
17	Erny et al. (2017)	Review	Animal	Microglia	Gut microbiota influence microglial maturation and activation.
21	Woolf (2011)	Review	Human	Central sensitization	Central sensitization is a key mechanism in pain amplification.
23	Latremoliere & Woolf (2009)	Review	Human/Animal	Pain hypersensitivity	Central sensitization generates persistent pain states.
24	Silva et al. (2020)	Review	Human/Animal	SCFAs	SCFAs regulate gut–brain signalling and neuronal activity.

Ref	Author (Year)	Study Type	Model/Population	Main Mechanism	Key Findings Relevant to Pain/Gut–Brain Axis
25	Dinan et al. (2013)	Review	Human	Psychobiotics	Probiotics may influence brain function and behaviour.
26	Distrutti et al. (2014)	Experimental Study	Animal	Probiotics	Probiotics reduce inflammation and improve gut barrier function.
27	Tracey (2002)	Conceptual Review	Human/Animal	Inflammatory reflex	Neural pathways regulate systemic inflammation.