Review

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Advances in the pathological mechanisms and clinical treatments of chronic visceral pain

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Abstract

Chronic visceral pain stems from internal organs and is frequently associated with functional gastrointestinal disorders, like irritable bowel syndrome (IBS). Since the underlying mechanisms of visceral pain remain largely unclear, clinical management is often limited and ineffective. Comprehensive research into the pathogenesis of visceral pain, along with the development of personalized therapeutic strategies, is crucial for advancing treatment options. Studies suggest that imbalances in purinergic receptors and neural circuit function are closely linked to the onset of visceral pain. In this review, we will explore the etiology and pathological mechanisms underlying visceral pain, with a focus on ion channels, epigenetic factors, and neural circuits, using functional gastrointestinal disorders as case studies. Finally, we will summarize and evaluate emerging treatments and potential initiatives aimed at managing visceral pain.

Keywords

Chronic visceral pain, irritable bowel syndrome, ion channels, epigenetic, neural circuit, clinical treatment

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Introduction

According to epidemiological studies, over 20% of adults globally suffer from chronic visceral pain, making it one of the leading reasons for seeking medical care. Visceral pain arises from nociception in the visceral organs of the thoracic or abdominal cavity and is distinct from somatic pain.[1–3] It is commonly associated with conditions such as acute or chronic pancreatitis, gallstones, and gastrointestinal (GI) disorders. Pain related to GI issues like inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), functional dyspepsia (FD), and other digestive disorders poses significant challenges for both patients and healthcare providers.[4,5] The mechanisms behind chronic visceral pain remain largely unknown, with symptoms that are often difficult to localize and describe, complicating both diagnosis and treatment. Furthermore, individuals suffering from chronic visceral pain frequently experience comorbid emotional, sleep, and cognitive disturbances, including anxiety, depression, fear, insomnia, and cognitive impairment.[6,7] These issues can heighten the perception of pain, creating a vicious cycle that drives up healthcare costs and severely impacts quality of life.[7–10] For example, IBS alone accounts for more than $350 million in direct healthcare

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expenses annually in the United States.[11] The current treatment for visceral pain mainly involves traditional medications like non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.[12] However, the ongoing opioid crisis further complicates pain management.[13] Therefore, there is an urgent demand to investigate the underlying mechanisms of visceral pain and develop novel analgesic drugs and treatment strategies.

The pathological mechanisms of chronic visceral pain are highly diverse, involving multiple processes in both the peripheral and central nervous systems.[2] For instance, the upregulation of P2X3R expression in the dorsal root ganglion (DRG) and 5-HT_{2B} expression in the thalamic nucleus reuniens (Re) has been shown to contribute to visceral pain behavior.[14,15] In this review, we will summarize recent advances in understanding chronic visceral pain, focusing on ion channels, epigenetic factors, and neural circuits. We will also explore potential clinical diagnostic and therapeutic strategies, with the goal of offering new insights into drug development and treatments for chronic visceral pain.

Ion channels in chronic visceral pain

Ion channels are crucial in the development and persistence of chronic visceral pain, they modulate pain perception by regulating neuronal excitability and signal transmission. Key ion channels involved in chronic visceral pain include ligand-gated ion channels, transient receptor potential (TRP) channels, potassium channels, and various regulatory mechanisms governing these channels.

Purine and pyrimidine receptors (P receptors) are classified into two main categories: P1 and P2 receptors.[16,17] P1 receptors, also known as adenosine receptors, are G-protein-coupled receptors, while P2 receptors are divided into two subgroups: P2X and P2Y receptors. P2X receptors function as ligand-gated ion channels, whereas P2Y receptors are also G-protein-coupled. ATP plays a significant role in chronic visceral pain pathophysiology.[14,18,19] Burnstock[20] proposed that epithelial cells in tubular and sac-like organs release ATP in response to distension, which activates P2X3 receptors in the submucosal nerve plexus, transmitting pain signals to the central nervous system. Galligan and Bertrand[21] demonstrated that ATP induces synaptic potentials in enteric neurons, while Ferguson et al.[22] showed that increased bladder hydrostatic pressure enhances ATP release from bladder epithelial cells. This effect is inhibited by the P2 receptor antagonist suramin, further supporting ATP's involvement in visceral pain signaling. Immunoreactivity of the P2X3 receptor has been observed in rat pelvic ganglion neurons, and P2X2 and P2X3 receptor immunoreactivities have been detected in guinea pig pelvic ganglion neurons.[23] Among P2X receptor subtypes, P2X4 homomers and P2X2/3 heteromers are thought to play a dominant role in chronic visceral pain.[24,25] Moreover, celiac ganglion neurons, which contain vagal afferent cell bodies, express functional P2X2 and P2X2/3 receptors, contributing to cardiovascular regulation and the transmission of angina.[23]

TRP channels are a class of non-selective cation channels located on cell and intracellular organelle membranes.[26–30] The TRP channel family is a superfamily, and current research identifies seven subtypes. The TRP channel family is a large superfamily, with seven identified subtypes. These channels are involved in a variety of signaling functions, including maintaining ionic balance, regulating intracellular organelles and stroke, and modulating sensory transmission related to pain, itch, temperature, taste, and vision.[29,31–39] Subfamilies of TRP channels, such as TRPV, TRPA, TRPC, and TRPM, have been shown to contribute to visceral pain signaling.[40] In line with spinal afferent-mediated pain, most TRP channels are associated with pain perception. Approximately 75% of chronic visceral afferent fibers express TRPV1, which is activated by capsaicin, suggesting that TRPV1 plays a dominant role in visceral afferent signaling and chronic visceral pain.[41] TRPA1 and TRPV1 channels coexist within visceral nociceptive fibers, working together to activate and modulate pain pathways. It has been confirmed that intestinal sensory neurons express multiple TRP channels. Research indicates that TRPA1, TRPV1, TRPV4, and TRPM8 may be co-expressed in the same neurons, acting synergistically in the nociceptive response. For example, in TRPA1 knockout mice, capsaicin no longer desensitizes colonic afferents, implying that TRPA1 channels are involved in the mechanical sensitivity mediated by TRPV1.[42] Furthermore, studies show that nociceptor activation and chronic pancreatitis pain are driven by nerve growth factor, which upregulates TRPV1 channels.[43] Neurons expressing TRPV1 can exacerbate experimental pancreatitis induced by various stimuli.[44] However, TRPV1 knockout mice are still affected, suggesting that overlapping mechanisms exist within these neurons and other TRP channels may also play significant roles. Encouragingly, drugs targeting TRPV1 such as capsaicin patch (8%) and capsaicin creams have been successfully used in the clinic with promising analgesic results.[45,46] Interestingly, the antagonist of TRPV1, PAC-14028, was found to have favorable therapeutic effects on itch,[47,48] suggesting that TRPV1-related drugs have great translational potential for both pain and itch.

Acid-sensing ion channels (ASICs) are trimeric protein complexes consisting of combinations of different subunits and are non-selective cation channels that are mainly expressed in the peripheral and central nervous systems.[49,50] Previous studies have shown that ASIC1 is expressed at high levels in the spinal cord dorsal horn in visceral pain rats, and inhibition of ASIC1 significantly alleviated visceral pain behaviors, suggesting that ASIC1 mediates the development of visceral pain.[51,52] Increasing evidence confirms that Piezo2 is dominantly expressed in DRG neurons and produces somatic mechanical allodynia in the context of tissue inflammation and nerve injury.[53,54] Recent study has shown that ablation of Piezo2 relieves visceral pain responses, suggesting that Piezo2 plays a key regulatory role in visceral pain and is a potential therapeutic target.[55] Additionally, many other ion channels such as Kv7.2, Hv1 and BK are involved in pain regulation.[56–60] Gaining a better understanding of

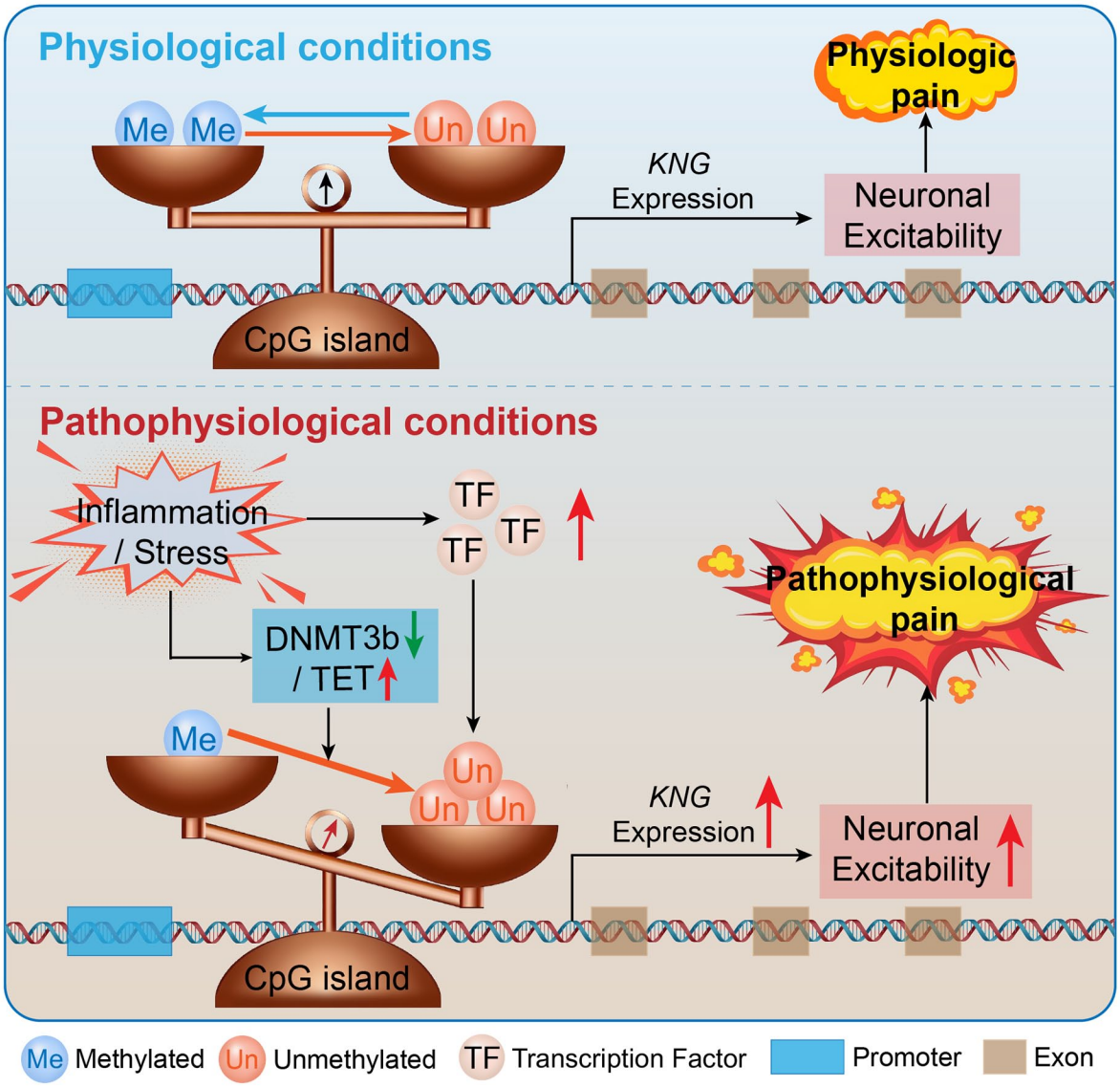

Figure 1. Schematic representation of DNA methylation and demethylation processes in physiological and pathological conditions.

these mechanisms could support the development of novel treatments, such as drugs that target specific ion channels, offering more effective pain relief for patients.

Epigenetics related to chronic visceral pain

Epigenetics refers to stable, heritable changes in gene function that occur without changes to the DNA sequence. These changes include DNA methylation, chromatin remodeling, and the actions of non-coding RNAs (ncRNAs).[61–63] Recent research on epigenetic mechanisms in chronic visceral pain has primarily focused on histone acetylation and DNA methylation, providing new insights into gene expression regulation related chronic visceral pain.

There is growing body of evidence that both DNA methylation and demethylation play significant roles in modulating pain sensation in both the peripheral and central nervous systems.[64] DNA methylation is controlled by several enzymes, including DNA methyltransferases like DNMT1, DNMT3a, and DNMT3b, as well as DNMT2 and DNMT3L family members.[65] Other studies indicate that promoting interactions between transcription factors and demethylated gene promoters in the peripheral nervous system may impact neuropathic pain and gastric hypersensitivity.[66–68] Research also indicates that GATA binding protein 1 (GATA1)-mediated DNA demethylation at the P2X7 receptor (P2X7R) locus could play a key role in the development of chronic visceral pain, as observed in neonatal colonic inflammation (NCI) model rats.[69] This process may involve a direct interaction with the Ten-eleven translocation 3 (TET3) demethylase (see Figure 1). Furthermore, a repeated water avoidance stress (WAS) regimen in female rats has

been shown to induce visceral pain hypersensitivity. This response is associated with increased acetylation of histone H3 in the spinal cord and an upregulation of mGlu2/3 receptor expression.[70]

Notably, the intrathecal administration of the histone deacetylase (HDAC) inhibitor SHA has been shown to reverse stress-induced visceral pain hypersensitivity.[71] Recent research also suggests that irritable bowel syndrome may have a heritable component due to epigenetic mechanisms. Specifically, the epigenetic regulation of pain-related genes in an adult IBS model is influenced by chronic stress experienced early in life. Pregnant rats subjected to intermittent heterotypic stress passed on heightened and persistent visceral pain sensitivity to their adult offspring when exposed to similar stress conditions.[72] Brain-derived neurotrophic factor (BDNF) has been identified as a key pain mediator, with elevated BDNF levels in the lumbar spinal dorsal horn strongly correlating with increased pain sensitivity compared to control groups.[73] Blocking the BDNF receptor TrkB or administering BDNF-siRNA, which inhibits BDNF expression, reduced visceral pain hypersensitivity in offspring rats.[74,75] These changes in BDNF expression were linked to an mRNA isoform originating from the first exon of the ninth core promoter, which showed increased binding sites for RNA polymerase II and acetylated histone H3, while showing decreased binding sites for HDAC1. In adult rats, daily administration of HAT inhibitors like curcumin or ACA reversed BDNF upregulation and the associated visceral pain behaviors. This finding suggests that histone acetylation plays a significant role in stress-induced visceral pain hypersensitivity passed down to offspring.[76] Tran et al. also utilized the WAS-induced visceral pain model to investigate the role of epigenetic modifications in stress-induced IBS visceral pain. They discovered that a 7-day intraventricular injection of the HDAC inhibitor TSA effectively reduced stress-induced visceral pain hypersensitivity.[70]

Additionally, there is increasing interest in the role of non-coding RNAs in the modulation of chronic pain, especially miRNAs.[77] Previous study has shown that miR-199 expression was significantly reduced in visceral pain model, whereas intraperitoneal injection of lenti-miR-199a precursors significantly alleviated visceral pain.[78] Similarly, miR-485 expression was significantly decreased in a rat model of visceral pain, and application of its corresponding agomir significantly alleviated visceral pain,[52] suggesting that different miRNAs regulate visceral pain with some degree of resemblance. Therefore, targeted modulation of miRNAs expression is an effective potential therapy for visceral pain. Interestingly, miRNAs are capable of acting on ion channels thereby modulating visceral pain. Previous study has identified miR-1306-3P as a potential endogenous ligand for P2X3R, which modulates visceral pain by altering P2X3R activity.[18] miR-485 also modulates visceral pain behavior by altering ASIC1 expression levels.[52]

Excitingly, recent studies have revealed that epigenetic modifications – such as histone methylation, N6-methyladenosine (m^6A) modification of RNA, and histone deacetylation – are critical in trigeminal neuropathic pain.[79–81] This highlights potential new therapeutic targets for treating neuropathic pain. However, it remains unclear whether similar epigenetic changes also influence visceral pain, which necessitates further investigation. While epigenetics offers exciting potential for studying chronic visceral pain, it also presents challenges. The complexity of epigenetic mechanisms requires the development of more precise experimental techniques to detect and explain relevant changes. Nevertheless, epigenetics provides new perspectives and tools for understanding chronic visceral pain. Future research is expected to uncover more detailed mechanisms, paving the way for personalized treatments and precision medicine in this field.

Neural circuits related to chronic visceral pain

Recent advances have greatly improved our understanding of the neural circuits and molecular mechanisms involved in chronic pain.[82–88] Multiple brain regions form neural circuits involved in the processing of pain signals.[89–91] However, the neural circuit mechanisms of chronic visceral pain remain largely unelucidated. Therefore, investigating the specific neural circuit mechanisms of visceral pain will hopefully provide suitable targets for the clinical treatment of chronic visceral pain.

Recent study evidenced that ventral part of lateral septum (LSV) was activated specifically by visceral pain stimulation and that optogenetic modulation of LSV glutamatergic neurons significantly altered visceral pain behavior in mice. This suggests that the LSV acts as a key regulatory center for visceral pain. Through viral tracing, it was found that the LSV forms a neural circuit with the paraventricular hypothalamus (PVH), and modulating this PVH-LSV circuit also affected visceral pain behaviors.[92] Recent study has demonstrated that P2X3R plays a decisive role in the modulatory effects of the PVH-LSV circuit on visceral pain, and that this pathway loses its function in modulating visceral pain after knockdown of P2X3Rs.[93] Moreover, the PVH-ventral tegmental area (VTA) neural circuit plays a significant role in controlling chronic visceral pain. When corticotropin-releasing hormone (CRH) neurons in the PVH were inhibited, it blocked the production of tyrosine hydroxylase in the VTA, which had been triggered by colorectal distension.[94] Evidence shows that CRH neurons in the PVH receive inputs from both glutamatergic and gamma-aminobutyric acid (GABA) neurons in the anterior ventral part of the bed nucleus of the stria terminalis (avBNST), and these inputs together regulate

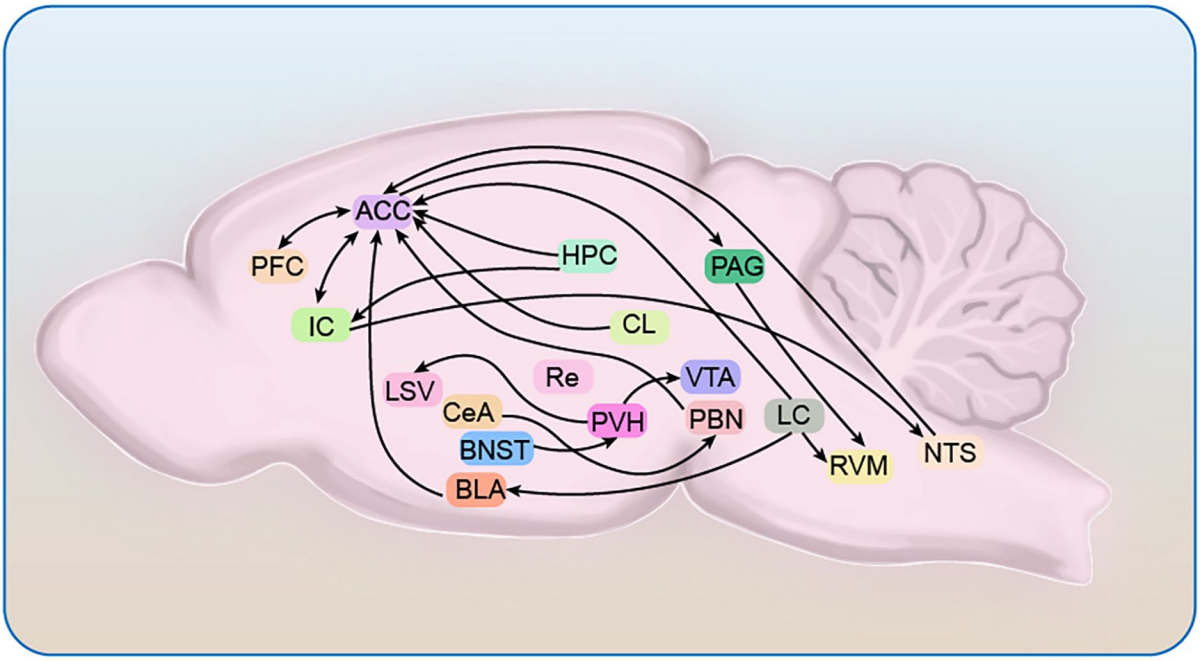

Figure 2. Summary schematic of neural circuits associated with visceral pain.
ACC: anterior cingulate cortex; BLA: basal lateral amygdala; BNST: bed nucleus of the stria terminalis; CeA: central amygdala; CL: claustrum; HPC: hippocampus; IC: insular cortex; LC: locus coeruleus; LSV: ventral part of lateral septum; NTS: nucleus of the solitary tract; PAG: periaqueductal gray; PBN: parabrachial nucleus; PFC: prefrontal cortex; PVH: paraventricular hypothalamus; Re: reuniens; RVM: rostral ventromedial medulla; VTA: ventral tegmental area.

visceral pain behaviors. Inhibiting the GABAergic neurons projecting from the BNST to the PVH worsened visceral pain, while activating this pathway alleviated it. Additionally, glutamatergic neurons in the avBNST send inputs to PVH CRH neurons.[95,96] Disruptions in the balance of excitatory and inhibitory inputs in the avBNST led to the overexcitation of PVH CRH neurons, which resulted in visceral pain behavior. Chemogenetic techniques were used to activate GABAergic neurons or inhibit glutamatergic neurons in the avBNST-PVH pathway, which reduced visceral pain in mice.[97] These studies highlight the importance of the PVH in developing and regulating visceral pain behavior, making it a key central hub for visceral pain regulation.

Previous studies have found that altered molecular expression in the anterior cingulate cortex (ACC) plays an important role in the processing of visceral pain, but the underlying neural circuitry mechanisms remain unclear.[8,98,99] However, accumulating evidence suggests that the ACC plays a dominant role in the neural circuits associated with visceral pain.[100–102] For instance, studies have demonstrated that the ACC responds more dramatically to colorectal distension stimulation in rats suffering from visceral pain, and functional magnetic resonance imaging (fMRI) data similarly show significant activation of the ACC in patients with irritable bowel syndrome.[100,103,104] The ACC receives a wide range of projections from other brain regions, forming neural circuits crucial for the modulation of chronic pain, including visceral pain.[84,100,105,106] Recent findings have revealed that glutamatergic neurons in the claustrum (CL) project to the ACC and mediate visceral pain behavior, although these neurons may not regulate inflammatory pain.[100,107] Xu et al.[100] identified positive responses from glutamatergic neurons in both the CL and ACC to visceral pain, and viral tracing confirmed anatomical connections between the two regions. Manipulation of the CL-ACC pathway significantly altered visceral but not somatic pain in mice, suggesting that this circuit is specifically associated with visceral pain.[100]

In addition to the PVH and ACC-related circuits, other brain regions such as the insular cortex, paraventricular thalamus, and reuniens (Re) have also been found to play important roles in the development of visceral pain behavior (see Figure 2).[12,15,108,109] Therefore, investigating the neural circuit mechanisms of visceral pain and developing therapeutic strategies based on these circuits may offer promising approaches for clinical treatment of visceral pain.

Analgesics associated with chronic visceral pain

Non-opioid analgesics. Acetaminophen has been widely used in the treatment of chronic pain, including chronic visceral

pain, primarily due to its antipyretic and analgesic properties. These effects occur through central and peripheral non-opioid mechanisms. Acetaminophen is the preferred class I analgesic for mild to moderate pain, according to the World Health Organization (WHO) pain ladder. It is a well-tolerated painkiller that is considered safe for managing mild to moderate visceral pain. However, it is crucial to adhere to dosage guidelines to avoid the risk of liver damage from excessive intake. Unlike nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen lacks anti-inflammatory effects.[110] NSAIDs have been reported to offer significant analgesic relief, especially in conditions like renal colic. However, due to their gastrointestinal side effects, including the potential for causing peptic ulcers and other lesions, NSAIDs are less commonly used for general visceral pain in clinical practice. In summary, acetaminophen is considered superior to NSAIDs for treating chronic visceral pain because it avoids the gastrointestinal side effects associated with NSAIDs, while maintaining a favorable safety profile. Acetaminophen can be used continuously when long-term analgesia is required.

Opioid analgesics. Opioids are frequently prescribed for patients with moderate to severe pain who do not respond to non-opioid treatments. They are also used for chronic visceral pain. Research indicates that morphine can increase the threshold for esophageal mechanical pain. In experimental pain tests involving patients with chronic pancreatitis, oxycodone was found to be more effective than morphine, as it raised both mechanical and thermal pain thresholds.[111] Additionally, current treatments can target peripheral kappa-opioid receptors (KORs). For example, the peripherally selective KOR agonist acimalalindol has been shown to alleviate pain caused by colonic dilation in people with irritable bowel syndrome.[112–114] Conversely, the loss of peripheral μ-opioid receptors (MORs) or the neurons expressing MORs reduces thermal tolerance, but does not affect the development or persistence of anti-allodynic tolerance or morphine-induced mechanical allodynia.[115] While opioids are a valuable and cost-effective option for treating organic visceral pain, their role in managing functional visceral diseases remains unclear. Opioids are associated with several serious side effects, including respiratory depression, motor and cognitive impairment, sedation, and the development of tolerance. Long-term use may also lead to opioid-induced hyperalgesia, where patients become more sensitive to pain. Additionally, chronic intractable pain can lead to changes in the central pain pathways, such as central sensitization, making opioid therapy less effective.[116]

Adjunctive analgesics. Many patients experience significant relief from standard analgesic interventions, but a considerable number continue to suffer from pain. To address this, incorporating adjunctive analgesics into a stepwise approach for managing chronic visceral pain is often effective. Introducing adjunctive analgesics early in the pain management process, especially when central sensitization manifests as hyperalgesia or touch-induced pain, can be crucial. At present, tricyclic antidepressants and GABA analogs are mostly utilized in clinical settings. Pregabalin and Gabapentin, two GABA analogs, have shown effectiveness in preclinical models of visceral hypersensitivity.[117–119] Pregabalin and Gabapentin have been shown to reduce experimental pain in chronic pancreatitis and IBS.[120] Additionally, other medications, such as tricyclic antidepressants (TCAs), selective serotonergic reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are also employed in the treatment of chronic visceral pain,[114] particularly for functional disorders. Adjunctive analgesics play a crucial role in managing visceral pain. It is essential to begin treatment with these adjuvants as early as possible, particularly when central sensitization is present.

Unconventional drug therapies. New analgesic drugs may soon be developed based on the growing understanding of the pain mechanisms of functional and organic visceral pain disorders. TRPV1 is a non-selective ion channel that can be activated by capsaicin, low pH, and nociceptive thermal stimuli. It is an integrator of pain stimuli, and as a result, TRPV1 antagonists have received increasing attention as novel analgesic agents.[121] Consequently, TRPV1 antagonists have gained significant attention as potential novel analgesics. The analgesic effects of TRPV1 antagonists have been demonstrated in several inflammatory diseases, including acute colitis and chronic pancreatitis (CP), where TRPV1 receptor sensitization may enhance peripheral sensitization.[2,122,123] Linaclotide is a guanylate cyclase-C agonist primarily used to treat constipation-type IBS.[124] By activating guanylate cyclase-C, it promotes the secretion of chloride and bicarbonate into the intestinal lumen, leading to increased fluid secretion and enhanced intestinal peristalsis. In addition to its laxative effect, recent studies have shown that linaclotide also exerts analgesic effects by blocking colonic nociceptors—a mechanism primarily validated in animal and in vitro models. Phase III clinical trials have further confirmed linaclotide's analgesic benefits in patients with constipation-predominant IBS.[125] Our previous study showed that P2X7R antagonists effectively suppressed chronic visceral pain behavior and inhibited spinal synaptic transmission.[69] Moreover, studies found that the P2X3 receptor inhibitor, TNP-ATP, can block acetic acid-induced abdominal spasms in rats and reduce visceral hypersensitivity caused by neonatal colon inflammation. These findings suggest that P2X receptors may serve as promising targets for novel analgesic therapies.[126,127]

Non-invasive brain stimulation in chronic visceral pain

Non-invasive brain stimulation (NIBS) has made significant strides in the treatment of chronic visceral pain.[128] Traditional treatment methods always have limited effectiveness and come with a higher risk of side effects, making NIBS an appealing alternative. As an emerging treatment modality, NIBS has garnered considerable attention. Studies have shown that both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) hold great promise for treating chronic visceral pain.[129] TMS generates magnetic fields in specific brain areas to modulate neuronal activity, thereby alleviating pain.[128,130,131] tDCS, on the other hand, alters the excitability of the cerebral cortex by applying a weak direct current to the scalp, aiming to relieve pain.[132] A recent clinical trial revealed that patients treated with TMS reported significant improvements in pain scores and quality of life.[133] Researchers have found that by precisely targeting specific brain regions associated with visceral pain, the regulation of pain activity can be more effective. Similarly, tDCS has shown positive effects in managing visceral pain caused by chronic pancreatitis, with patients reporting significant reductions in pain levels without notable side effects.[134] Beyond TMS and tDCS, other NIBS technologies are being continuously developed. For instance, transcranial random noise stimulation (tRNS) and transcranial alternating current stimulation (tACS) are emerging approaches that are gradually being applied to the treatment of chronic visceral pain.[135] Interestingly, Zhou et al.[136] demonstrated that sound induces analgesia through corticothalamic pathway and found that the analgesic effects of sound depended on a low (5-decibel) signal-to-noise ratio relative to ambient noise. Although the applicability of sound analgesia to visceral pain remains unclear, this provides an essential insight into the development of non-invasive brain stimulation for the treatment of visceral pain. These techniques modulate brain activity through different mechanisms, offering patients a wider range of treatment options. Additionally, accumulating evidence suggests that non-pharmacological therapies such as psychotherapy and dietary adjustment show considerable potential in the treatment of chronic visceral pain.[137–139] Previous study has demonstrated that the combined employment of psychotherapy and drugs is significantly more effective in the treatment of IBS than drugs alone,[137] suggesting that psychotherapy may be a catalyst for the conventional pharmacological treatment of IBS. As an essential regulator of normal gut function, the gut microbiota is considered a key peripheral factor in the pathophysiology of chronic visceral pain. As diet is a major determinant of the configuration of the gut microbiota, it is increasingly recognized that the interaction between diet and microbiota plays an essential role in the development of visceral pain, and that dietary adjustment is an effective way to alleviate visceral pain.[140] In addition, it has been shown that gastrointestinal hypersensitivity is also caused by the activation of enterochromaffin (EC) cells, which are rare excitable, serotonergic neuroendocrine cells in the gut epithelium.[141,142] Additionally, perturbing EC cell activity promoted anxiety-like behaviors which normalized after blockade of serotonergic signaling,[7] suggesting that anxiety relief by targeting serotonergic signaling pathways is a potential modality for the treatment of visceral pain. The combination of non-invasive brain stimulation technologies with non-pharmacological therapies contributes to a multi-dimensional pain management framework.

Despite the promising potential of NIBS technologies, several challenges remain. Determining optimal stimulation parameters, improving individualized treatment approaches, and validating long-term efficacy are areas that need further research. Addressing these challenges will be crucial for the broader application of NIBS in chronic visceral pain treatment. In conclusion, NIBS technologies bring new hope for the management of chronic visceral pain. With ongoing research and technological advancements, these techniques hold great potential to deliver significant clinical benefits, improving the quality of life for more patients.

Conclusions

The pathology of visceral pain is highly complex, and its exact mechanisms have not yet been fully elucidated. In this review, we analyze the intrinsic mechanisms of visceral pain from various perspectives, including ion channels, epigenetics, neural circuits, analgesics and non-invasive brain stimulation with the goal of offering new insights into potential treatments (see Figure 3). Historically, much research on the signaling and regulatory mechanisms of visceral pain has focused on the peripheral and spinal cord levels. However, the rapid advancements in neural circuit studies have provided fresh perspectives on the brain's role in visceral pain. Despite this progress, the specific molecular targets and neural circuits related to visceral pain remain incompletely understood, presenting significant challenges for developing targeted treatments. Encouragingly, the rapid development of modern neuroscience techniques has made function-dependent labeling and modulation tools increasingly precise. For example, the "targeted recombination in active populations" (TRAP) labeling system and the "Tet-off" viral labeling system enable the specific manipulation of neurons activated by visceral pain.[93] These tools hold great promise for future studies aimed at identifying molecular targets and neural circuits directly associated with visceral pain. In conclusion, significant progress has been made in the development of therapeutic drugs and approaches for visceral pain. However, limitations and challenges remain, underscoring the need for further research and exploration in this field.

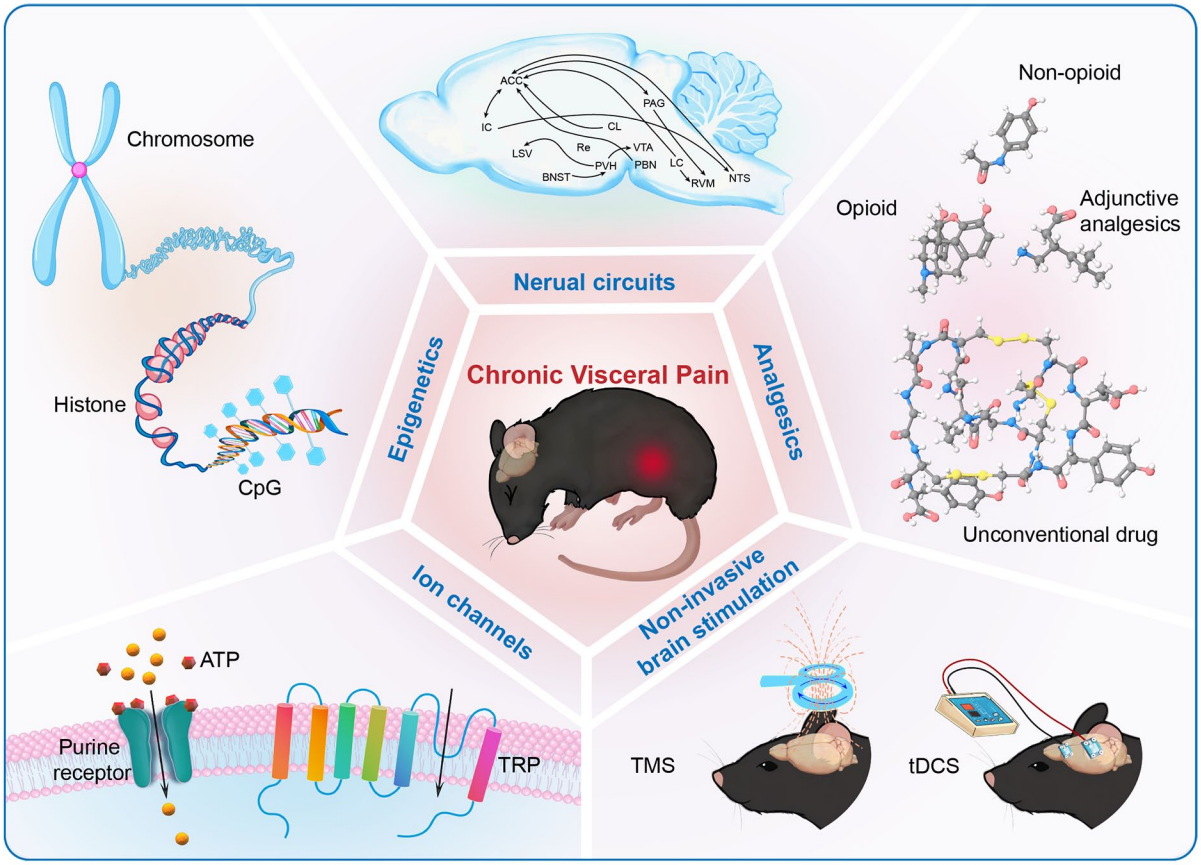

Figure 3. Summary schematic of ion channels, epigenetics, neural circuits, analgesic drugs, and noninvasive brain stimulation associated with visceral pain.
ACC: anterior cingulate cortex; BNST: bed nucleus of the stria terminalis; CL: claustrum; CpG: cytosine- phosphoric acid- guanine; IC: insular cortex; LC: locus coeruleus; LSV: ventral part of lateral septum; NTS: nucleus of the solitary tract; PAG: periaqueductal gray; PBN: parabrachial nucleus; PVH: paraventricular hypothalamus; Re: reuniens; RVM: rostral ventromedial medulla; tDCS: transcranial direct current stimulation; TMS: transcranial Magnetic Stimulation; TRP: transient receptor potential; VTA: ventral tegmental area.

Author contribution

Y-C.L, F-C.Z and T-W.X collected data and prepared the manuscript. R-X.W, H-H.Z, Q-Q.C, S-F.H, Y.G and R.L revised the manuscript. G-Y.X designed the research plan, supervised writing and finalized the manuscript. All the authors have read and approved the paper.

Declaration of conflicting interests

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