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Advances in GLP-1 receptor agonists for pain treatment and their future potential

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) show substantial efficacy in regulating blood glucose levels and lipid metabolism, initially as an effective treatment for diabetes mellitus. In recent years, GLP-1RAs have become a focal point in the medical community due to their innovative treatment mechanisms, robust therapeutic efficacy, and expansive development prospects. Notably, GLP-1RAs benefit pain management through their neuroprotective and metabolic regulatory properties, such as inhibiting inflammation responses and oxidative stress, promoting β-endorphin release and modulating several other crucial biological pathways. Hence GLP-1RAs hold promise for repurposing as treatments for pain disorders. In this narrative review, we thoroughly trace the current preclinical and clinical evidence of seven pain modalities, including inflammatory pain, osteoarthritis, visceral pain, neuropathic pain, diabetic neuropathy, cancer pain and headache, to support the efficacy and underlying biological mechanisms of GLP-1RAs as therapeutic agents for pain suffering. Despite these promising findings, further research is necessary to establish their long-term efficacy, optimal dosing strategies, and potential synergistic interactions of GLP-1RAs with existing pain management therapies. Future clinical trials should aim to distinguish the direct analgesic effects of GLP-1RAs from their metabolic benefits and explore their broader applications in pain conditions. The ongoing exploration of new indications for GLP-1RAs further highlights their transformative potential in advancing medical treatments across diverse clinical fields.

Keywords GLP-1RAs, Inflammatory pain, Osteoarthritis, Visceral pain, Neuropathic pain, Diabetic neuropathy, Headache, Cancer pain

Introduction

GLP-1RAs are a class of pharmacological agents employed in managing two highly prevalent metabolic disorders worldwide: type 2 diabetes mellitus (T2DM) and obesity [1]. GLP-1, an originally identified natural prototype, is synthesized and secreted by intestinal enteroendocrine L-cells and certain neurons within the nucleus of the solitary tract in the brainstem [2]. Its release is stimulated by nutrient ingestion and neuroendocrine stimulation, eliciting several key metabolic responses, including enhanced insulin secretion, suppressed glucagon release, delayed gastric emptying, and increased satiety through both peripheral and central mechanisms [1]. Nevertheless, GLP-1 presented a rather ephemeral circulatory half-life, lasting a mere 1–2 min, due to the rapid enzymatic degradation by dipeptidyl peptidase IV (DPP-4), which markedly limits its biological efficacy [3–5]. To overcome this limitation, GLP-1 analogs have undergone extensive structural modifications to render them resistant to degradation while

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replicating the pharmacological functions [6, 7]. At present, several GLP-1 analogs have joined the class, such as exenatide, liraglutide, dulaglutide, semaglutide and tirzepatide [1].

Glucagon-like peptide-1 receptor (GLP-1R), a class B G-protein-coupled receptor (GPCR), is broadly expressed on the surfaces of various cells, including the pancreas, intestine and brain [8]. Upon activation by GLP-1RAs, GLP-1R initiates diverse intracellular cascades, such as the cyclic adenosine monophosphate (cAMP) / protein kinase A (PKA) pathway and phosphatidylinositol 3-kinase (PI3K) / protein kinase B (Akt) signaling pathway [1, 9]. These pathways underpin the wide-ranging therapeutic benefits, extending the benefits of GLP-1RAs beyond conventional glucose management. Notably, GLP-1R is abundantly expressed in various brain regions, including the hypothalamus, cortex, and hippocampus, as well as peripheral nervous tissues [10]. This distribution enables GLP-1RAs to exert significant neurobiological effects. They have been implicated in promoting neuroprotection, improving neurological structure and functions, attenuating apoptosis, mitigating oxidative stress, and modulating neuroinflammation [11–13]. Deficiency or dysregulation of GLP-1R has been linked to behavioral, mood, and cognitive disturbances [14, 15]. Recent preclinical andclinical studies have demonstrated the significant potential of GLP-1RAs in slowing the progression of neurodegenerative diseases [16, 17]. For example, GLP-1RAs were proven in the clinic to slow the disease progression of Alzheimer's disease and Parkinson's disease, attributed in part to their anti-inflammatory and neuroprotective properties [16, 18–22]. These findings highlight the capacity of GLP-1RAs to extend their therapeutic impact well beyond traditional metabolic targets. Additionally, GLP-1RAs may influence other neurological functions, *inter alia* in pain modulation. Several preclinical models and clinical studies also suggest their potential as a novel therapeutic strategy for managing pain symptoms. As GLP-1RAs continue to garner increasing interest in pain research, Halloum et al. have reviewed their role in pain modulation [23]. However, the studies often take a broad landscape, lacking a detailed analysis of the specific roles and limitations of GLP-1RAs across different pain conditions. A more comprehensive and systematic evaluation is needed to elucidate their underlying mechanisms, therapeutic potential, and challenges that must be addressed to maximize their efficacy across various pain modalities.

Consequently, the present review aims to more comprehensively summarize the current understanding of the involvement of GLP-1RAs across distinct categories of pain, elucidate their mechanisms of action, and shed light on the future direction of clinical investigations by incorporating findings from newly published studies on GLP-1RAs in pain modalities. A schematic diagram illustrating the diverse pain modalities and their associated mechanisms is presented in Fig. 1.

Inflammatory pain

GLP-1(7–36)-amide, the major biologically active form of GLP-1, retains detectable biological activity. In 2014, an influential study by Wang et al. serendipitously discovered that GLP-1(7–36) exerts potent antinociceptive effects in the formalin test, prompting a systematic investigation of its role in alleviating pain hypersensitivity and its underlying mechanisms [24]. Subsequently, in murine formalin models, intrathecal injection of GLP-1(7–36) at a variety of doses significantly reduced the tonic flinching response in a dose-dependent manner, with no effects on acute nociceptive responses [24]. This antinociceptive effect was completely abolished by GLP-1R antagonism, underscoring its receptor-mediated effects [24] (Fig. 2A). Additionally, GLP-1 and its homolog GLP-2 exhibited inhibitory effects on nociceptive pain induced by thermal and chemical stimuli [25]. Exenatide is a GLP-1 analog, derived from exendin-4 and originally isolated from the salivary secretions of the Gila monster [26]. Intrathecal injection of exenatide (1-100 ng) elicited dose-dependent antinociception in formalin-induced tonic flinching responses without affecting acute nociceptive phases [24] (Fig. 2A). In contrast, intracerebroventricular injection, even at doses up to 300 ng, failed to influence acute or tonic flinching responses [24]. Evidence from receptor blockade and GLP-1R gene knockdown experiments confirmed that the spinal cord is a primary site mediating exenatide-induced antinociception [24]. Mechanistically, exenatide stimulated the release of β-endorphin from spinal cord tissue and cultured primary microglia. The antinociceptive effect was completely blocked by minocycline (a microglial inhibitor), β-endorphin antiserum, or naloxone (an opioid receptor antagonist) [24]. Exendin 9–39, a synthetic peptide derived from exendin-4 via N-terminal truncation and sharing 53% sequence homology with GLP-1, functions as a specific and competitive antagonist of GLP-1R [27]. Recent studies have shown that both exendin-4 and exendin 9–39 effectively reduce capsaicin-induced acute pain and chronic pain caused by Complete Freund's Adjuvant (CFA) in mice [28] (Fig. 2B). Interestingly, exendin 20–29, a fragment of exendin 9–39, directly and specifically inhibits transient receptor potential vanilloid 1 (TRPV1) activity in sensory neurons, thereby alleviating pain behaviors [28]. Liraglutide, a GLP-1 analog with an extended half-life, has also demonstrated efficacy in reducing pain hypersensitivity. In a rat model of carrageenan-induced acute peripheral inflammation, liraglutide significantly reduced hypersensitivity to mechanical and cold stimuli through its anti-inflammatory effects, notably by

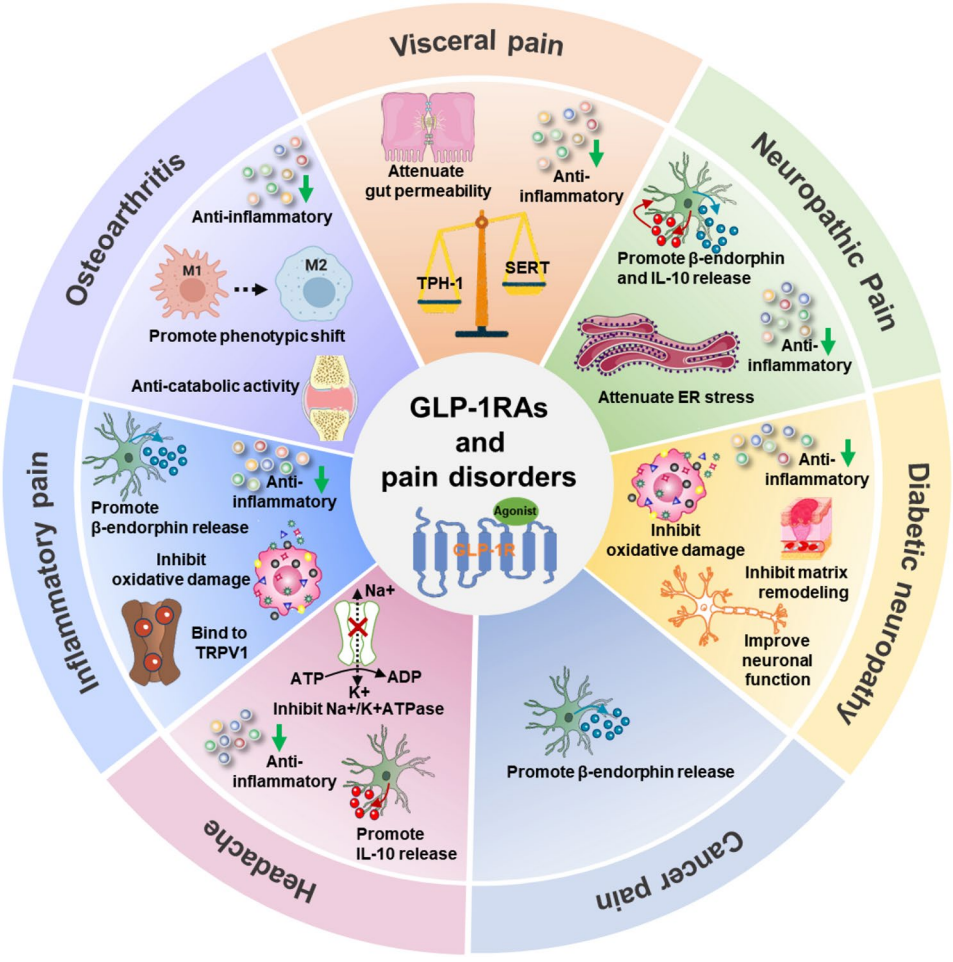

Fig. 1 Schematic illustration of potential mechanisms of GLP-1RAs in pain management. GLP-1RAs alleviate pain through neuroprotective and metabolic regulatory effects, including anti-inflammatory and antioxidant actions, β-endorphin release, and modulation of key pain-related pathways. Abbreviations: GLP-1RAs: glucagon-like peptide-1 receptor agonists; GLP-1R: glucagon-like peptide-1 receptor; TRPV1: transient receptor potential vanilloid 1; TPH-1: tryptophan hydroxylase-1; SERT: serotonin transporter; ER: endoplasmic reticulum; IL-10: interleukin-10

increasing interleukin-10 (IL-10) levels and suppressing tumor necrosis factor-α (TNF-α) expression in inflamed tissue [29] (Fig. 2C). Additionally, intraperitoneal injection of liraglutide reduced nociceptive behavior in the formalin test, particularly during the second phase [30]. Beyond peptide agonists, non-peptide GLP-1R agonists like WB4-24 have also shown promise. WB4-24 exhibited dose-dependent and specific anti-hypersensitive effects in acute and chronic inflammatory nociception induced by formalin, carrageenan, and CFA [31]. This effect was mediated through the release of β-endorphin rather than suppression of proinflammatory cytokine expression in spinal microglia [31] (Fig. 2D). Natural product-derived components have also been identified as potential small-molecule GLP-1R agonists. Geniposide, a primary iridoid glycoside from *Gardenia jasminoides*, has long been used in traditional Chinese medicine for its homeostatic, anti-inflammatory, antinociceptive, and antipyretic properties [32]. Orally administered geniposide and its iridoid analogs exhibit antinociceptive effects in the formalin-induced tonic flinching response via activation of spinal GLP-1Rs, potentially targeting the same binding sites as exendin (9–39) and exenatide [33]. Finally, the DPP-4, responsible for degrading biologically active peptides like opioids and GLP-1, has emerged as a target for enhancing GLP-1 levels [7, 34, 35]. DPP-4 inhibitors, such as diprotin A, vildagliptin, and evogliptin tartrate, exhibit analgesic effects in rat models of carrageenan-induced sub-chronic inflammatory pain, as well as acute and tonic pain induced by CFA and formalin [36, 37]. A brief description of this section is listed in Table 1.

Osteoarthritis

Osteoarthritis (OA), particularly of the knee, is the most prevalent form of arthritis, characterized by chronic pain and physical disability [36, 38]. Obesity is a well-established risk factor for the development and progression of knee OA (KOA). Epidemiological evidence demonstrates

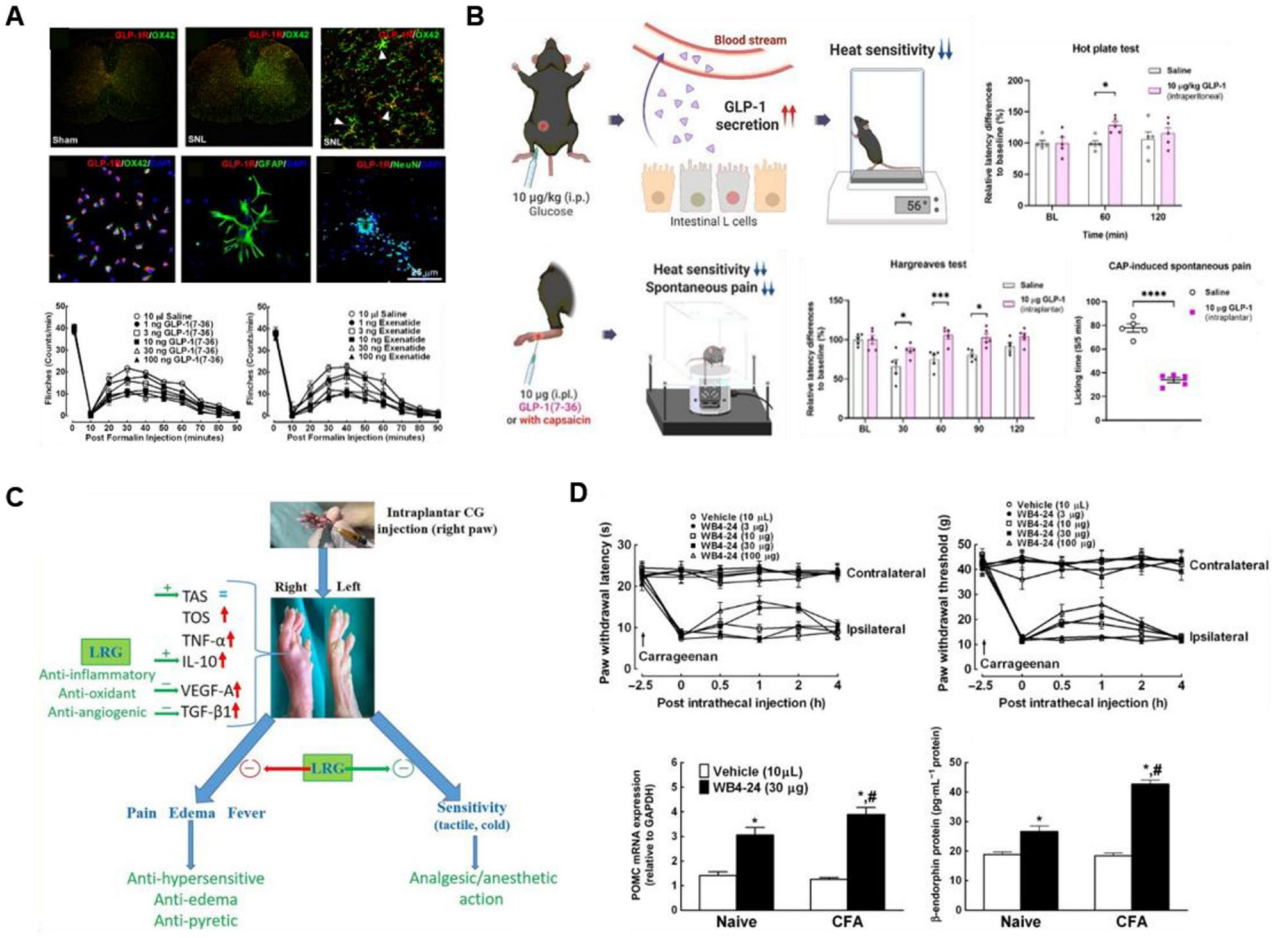

Fig. 2 (**A**) GLP-1R expression in the microglia and effects of intrathecal injection of GLP-1(7–36) and exenatide on formalin-induced flinching response. Reproduced under terms of the CC-BY 4.0 license [24]. Copyright 2014, Society for Neuroscience. (**B**) Reduced thermal sensitivity in systemically glucose or GLP-1 treated- and locally GLP-1 treated mice and analgesic effect of GLP-1 on capsaicin-induced nociceptive behaviors. Reproduced under terms of the CC-BY 4.0 license [28]. Copyright 2014, Society for Neuroscience. (**C**) Schematic representation of the suppressive action mechanisms of liraglutide in carrageenan-induced hypersensitivities, edema and fever. Reproduced with permission [29]. Copyright 2022, Springer Nature. (**D**) Antinociceptive effects of intrathecal injection of WB4-24 on thermal hyperalgesia and mechanical allodynia induced by carrageenan and the expression of β-endorphin in naive rats and CFA-treated rats. Reproduced with permission [31]. Copyright 2014, The British Pharmacological Society

a strong association between obesity and KOA, highlighting shared pathogenic mechanisms. The onset of one condition can increase the risk of the other, potentially creating a self-reinforcing cycle of disease progression [39, 40]. Given this interplay, weight loss is a cornerstone of managing patients with coexisting obesity and KOA. Evidence indicates that weight reduction not only alleviates pain but also enhances physical function, underscoring its critical role in breaking the vicious cycle between these conditions [41–44]. In a murine model of OA induced by sodium monoiodoacetate (MIA), intra-articular administration of liraglutide effectively mitigated OA-associated pain [45]. Complementary in vitro studies revealed that liraglutide exerted a dose-dependent inhibitory effect on the secretion of pro-inflammatory mediators, including interleukin 6 (IL-6), prostaglandin E2 (PGE2), and nitric oxide (NO), and suppressed the expression of inflammatory genes in chondrocytes and macrophages [45]. Furthermore, liraglutide promoted a phenotypic shift in polarized macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype [45]. This immunomodulatory effect was accompanied by significant anti-catabolic activity, as liraglutide reduced the activity of metalloproteinases and aggrecanases-key enzymes responsible for cartilage degradation [45] (Fig. 3). In a surgically induced-OA model in rats, liraglutide also attenuated rat cartilage degeneration through suppressing the release of inflammatory mediators and protected chondrocytes against endoplasmic reticulum (ER) stress and apoptosis induced by interleukin-1β (IL-1β) or triglycerides [46].

Human studies on the analgesic efficacy of liraglutide in KOA have yielded inconclusive results. The observed clinical benefits appear to stem primarily from weight

Table 1 Preclinical evidence of GLP-1RAs for treating inflammatory pain

Compound	Model	Key findings	Ref.
GLP-1 (7–36)	Formalin induced-pain in mice and rats	GLP-1(7–36) reduced tonic flinching response	[24]
GLP-1 and GLP-2	Formalin induced-pain in mice	GLP-1 and GLP-2 produced analgesic effects through different pathways	[25]
Exenatide	Formalin induced-pain in mice and rats	Exenatide evoked microglial β-endorphin release	[24]
Exendin 20–29	Capsaicin and CFA induced-pain in mice	Exendin 20–29 directly bound to TRPV1	[28]
WB4-24	Formalin, carrageenan or CFA induced-pain in rats	WB4-24 evoked β-endorphin release	[31]
Geniposide	Formalin induced-pain in mice and rats	Geniposide and its iridoid analogs inhibited oxidative damage	[33]
Evogliptin tartrate	CFA induced-pain in rats	Evogliptin tartrate mirrored the anti-inflammatory pain relief of indomethacin	[36]
Diprotin A and Vildagliptin	CFA and formalin induced-pain in rats	Diprotin A and vildagliptin display antinociception of different mechanisms of action	[37]

loss rather than direct analgesic mechanisms. For example, a randomized, double-blind, placebo-controlled trial in patients with overweight or obesity -associated KOA assessed the effects of liraglutide (3 mg/day) over 52 weeks as an add-on to dietary guidance [47, 48]. The co-primary outcomes were changes in body weight and the Knee Injury and Osteoarthritis Outcome Score pain subscale from week 0 to 52 [47, 48]. Results highlighted that liraglutide induced significant weight loss but did not reduce knee pain compared to placebo [48]. Additionally, a large-scale observational study involving over 40,000 Chinese OA patients with comorbid T2DM reported that GLP-1RA therapies offered disease-modifying benefits [49]. These benefits included reduced cartilage loss velocity and a lower need for intra-articular steroid injections. However, the direct effects of GLP-1RAs, independent of weight loss, were not statistically significant [49]. Dulaglutide, a once-weekly GLP-1RA, demonstrated significant improvements in glycemic control, knee OA pain, weight management, and reduced NSAID usage in elderly T2DM patients with bilateral KOA [50]. Mechanistically, dulaglutide downregulates matrix metalloproteinases (MMP-3 and MMP-13) and aggrecanases, protecting the articular extracellular matrix [50]. Additionally, it suppresses pro-inflammatory cytokines and chemokines via the NF-κB pathway while reducing reactive oxygen species (ROS) production [51]. Another long-acting GLP-1RA, semaglutide, was evaluated in a 68-week, randomized, placebo-controlled trial across 61 sites in 11 countries [52]. Participants with obesity (body mass index (BMI) ≥ 30 kg/m²) and moderate-to-severe KOA pain experienced significantly greater reductions in body weight and OA-related pain with weekly semaglutide injections compared to placebo [52]. A brief description of this section is listed in Table 2.

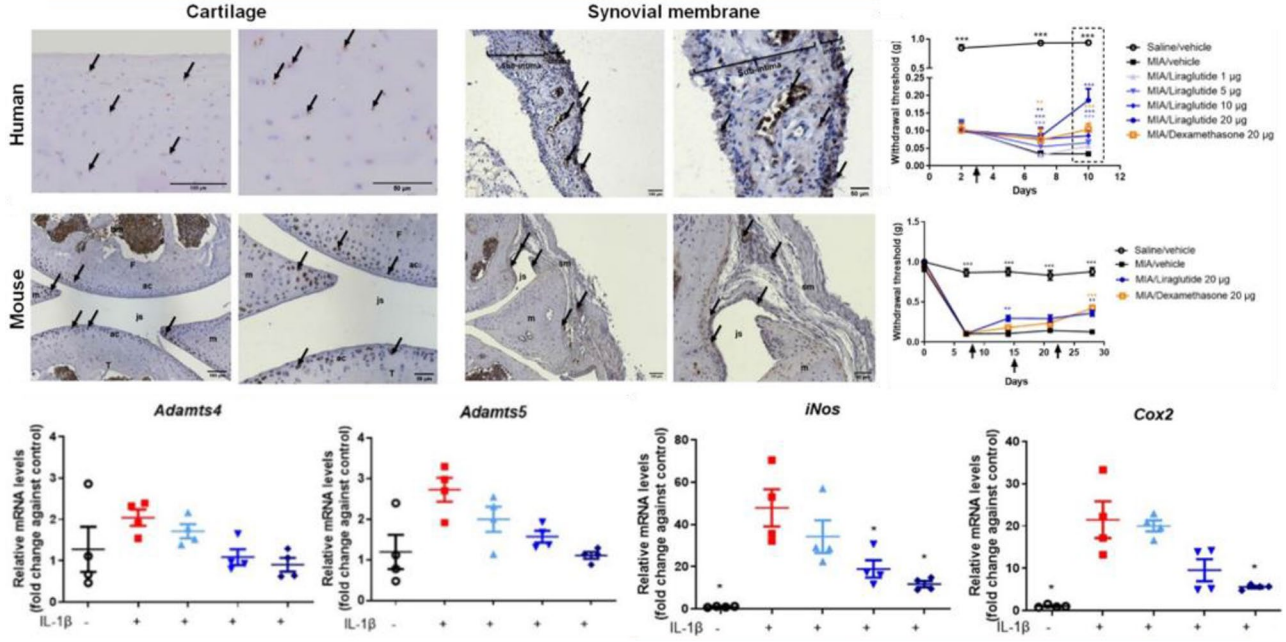

Fig. 3 Expression of GLP-1R in OA human and non-OA mouse knee joint and liraglutide exerted analgesic effect via anti-inflammatory and anti-degradative actions. Reproduced with permission [45]. Copyright 2022, Springer Nature

Table 2 Preclinical and clinical evidence of GLP-1RAs for OA-related pain treatment

Compound	Model/Disease	Key findings	Ref.
***In vitro*evidence**			
Dulaglutide	Human SW1353 chondrocytes	Dulaglutide ameliorated the articular extracellular matrix and suppressed the expression of pro-inflammatory cytokines, chemokines and ROS via NF-κB pathway	[51]
***In vivo*evidence**			
Liraglutide	Intra-articular MIA-induce OA in mice	Liraglutide exerted anti-inflammatory and anti-catabolic activity	[45]
Liraglutide	Surgically induced-OA in rats	Liraglutide attenuated cartilage degeneration in knee joints	[46]
Clinical evidence			
Liraglutide	Overweight or obesity with knee OA	A 52-week treatment with 3 mg/day liraglutide-caused weight loss and improved KOA-related pain symptoms	[47]
GLP-1RAs	T2DM with knee OA	Reduced incidence of knee surgery associated with GLP-1RA exposure was due to weight loss, not glycemic control	[49]
Dulaglutide	T2DM with knee OA	Dulaglutide improved glycemic control, knee joint OA pain and weight management	[50]
Semaglutide	Obesity with knee OA	Treatment with once-weekly semaglutide reduced body weight and KOA related-pain	[52]

Abbreviations: GLP-1RAs: glucagon-like peptide-1 receptor agonists; OA: osteoarthritis; KOA: knee osteoarthritis; MIA: monoiodoacetate; ROS: reactive oxygen species; NF-κB: nuclear factor kappa-B; T2DM: type 2 diabetes mellitus

Visceral pain and irritable bowel syndrome

Irritable bowel syndrome (IBS) is primarily characterized by chronic abdominal pain or discomfort. Accumulating evidence implicates visceral hypersensitivity, abnormal gastrointestinal motility, inflammation, and/or infection of the gut in its pathophysiology [53]. Among these, visceral hypersensitivity is a hallmark biological feature of IBS, which manifests as pain associated with bowel disturbances [54]. It was reported that GLP-1R was expressed in colonic mucosal nerve fibers and showed increased expression in biopsies from individuals with IBS [55] (Fig. 4A). Treatment with GLP-1 and exendin-4 significantly increased neurite length in cultured DRG neurons, potentially accounting for the increased nerve fibers observed in IBS biopsies [55] (Fig. 4A). While adenosine triphosphate (ATP) signaling was enhanced in cultured DRG neurons treated with exendin-4, capsaicin sensitivity and calcium influx remained unaffected, suggesting GLP-1R predominantly modulating gut motility rather than pain signaling [55]. In addition, in a rat model of IBS, intraperitoneal administration of exendin-4 normalized stress-induced defecation and visceral pain sensitivity, without affecting centrally regulated anxiety-like behaviors [56]. These benefits are possibly attributed to the modulation of enteric neuronal function and tight junction expression by exendin-4, as evidenced by reduced occludin levels [56]. Another study in colonic-sensitized rat models demonstrated that exendin-4 treatment dose-dependently reduced visceral hypersensitivity by upregulating serotonin transporter (SERT) expression and downregulating tryptophan hydroxylase-1 (TPH-1) expression [57]. Further in vitro studies in IEC-6 cells revealed that exendin-4 enhanced SERT expression and increased 5-HT reuptake [58] (Fig. 4B). This effect was mediated via adenylate cyclase (AC) / PKA signaling pathway, as it was abolished by the GLP-1R inhibitor exendin-9, or by PKA inhibitors SQ22536 and H89 [58]. In a model of lipopolysaccharide (LPS)-induced visceral hypersensitivity and repeated water avoidance stress (WAS) in rats, liraglutide effectively reduced visceral allodynia by suppressing pro-inflammatory cytokine production and improving colonic barrier integrity [59]. Specifically, liraglutide inhibited IL-6 levels in colonic mucosa via a NO-dependent mechanism [59] (Fig. 4C). ROSE-010, a GLP-1 analog, displayed a therapeutic potential for abdominal pain in the clinic. A randomized, double-blind, placebo-controlled study demonstrated that ROSE-010 was well tolerated and provided rapid and effective relief of acute pain attacks in IBS patients [60]. Additionally, patients with constipation-predominant IBS (IBS-C) exhibit significantly lower serum GLP-1 levels, which negatively correlate with abdominal pain scores. Colonic biopsies from these patients also show reduced GLP-1R expression, suggesting that decreased GLP-1 and GLP-1R expression may underlie the efficacy of ROSE-010 in alleviating IBS-C abdominal pain [61]. An exploratory clinical sub-study analyzed data from 166 participants (116 females, 50 males) to identify the most responsive subpopulations to ROSE-010 treatment for IBS-related pain [62]. Participants received ROSE-010 at doses of 100–300 μg, or placebo [62]. The findings revealed that ROSE-010 produced dose- and time-dependent pain relief, with 300 μg showing the greatest efficacy, where the maximum pain relief occurred at 120 min post-injection. Additionally, females experienced greater pain relief than males, suggesting a potential gender-specific response to the treatment [62]. Neither age nor BMI influenced the treatment's effectiveness [62]. They also found that ROSE-010 was most effective in patients with constipation-dominant IBS (IBS-C) and mixed IBS, with significantly less pain relief observed in patients

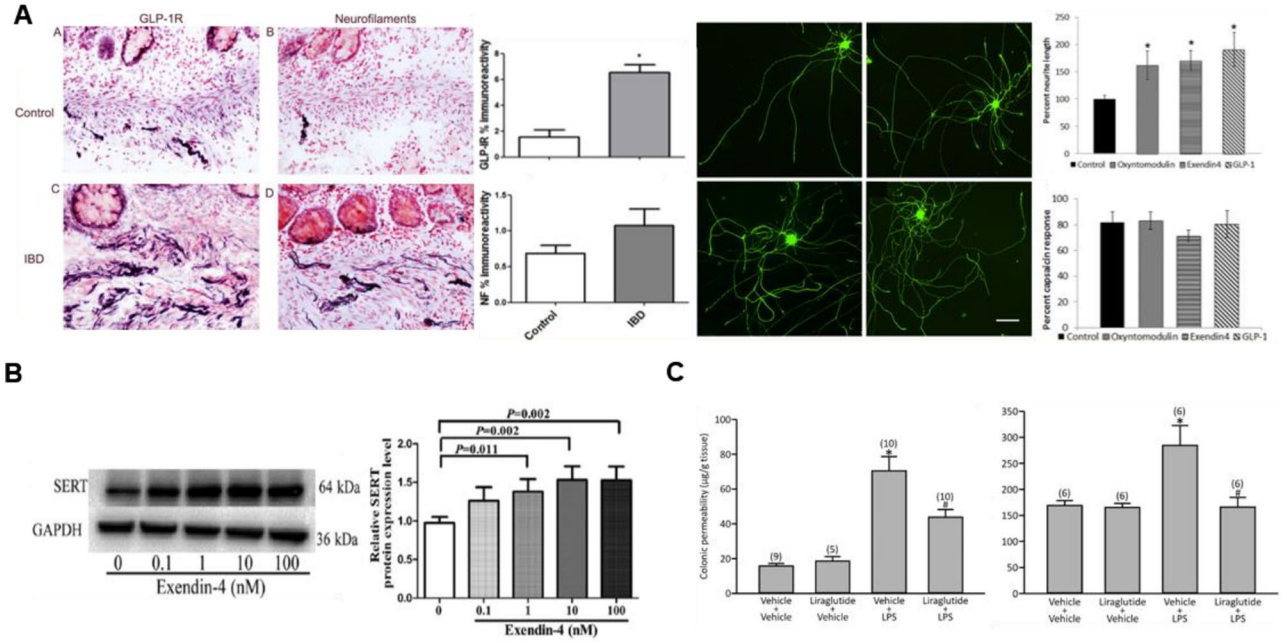

Fig. 4 (**A**) GLP-1R expressed in colonic mucosal nerve fibers of IBD biopsies and treatment with exendin-4 and GLP-1 increased neurite length in cultured neurons. Reproduced under terms of the CC-BY 4.0 license [55]. Copyright 2018, Public Library of Science. (**B**) Effects of exendin-4 on SERT expression in ICE-6 cells. Reproduced under terms of the CC-BY 4.0 license [58]. Copyright 2020, D. A. Spandidos. (**C**) Liraglutide inhibited the expression of IL-6 and attenuated the increased gut permeability. Reproduced with permission [59]. Copyright 2017, John Wiley and Sons

with diarrhea-dominant or unspecified IBS [62]. A brief description of this section is listed in Table 3.

Neuropathic pain

Emerging evidence underscores the critical role of GLP-1RAs in neuropathic pain regulation by modulating several crucial biological pathways. In a rat model of spinal nerve ligation (SNL), exenatide significantly enhanced the expression of M2 microglial markers, including IL-10, IL-4, Arg1, and CD206, in both spinal microglia and primary cultured microglia [63]. Intrathecal administration of exenatide upregulated IL-10 and β-endorphin expression in spinal microglia of neuropathic rats [63]. In vitro, IL-10 treatment directly stimulated β-endorphin expression in primary microglia [63]. Blockade of IL-10 with a neutralizing antibody fully inhibited exenatide-induced β-endorphin expression both in vitro and in vivo, effectively abolishing its mechanical antiallodynic effects in neuropathic rats [63]. Herein, exenatide-induced IL-10 expression was dependent on the cAMP/PKA/p38β/CREB signaling axis [63]. Pharmacological inhibitors and siRNA-mediated knockdown of p38β completely suppressed IL-10 production in primary cultured microglia [63]. β-endorphin expression was mediated through autocrine activation of the IL-10 receptor-α and downstream phosphorylation of STAT3 [63]. Knockdown of IL-10 receptor-α or pharmacological inhibition of STAT3 activation abolished exenatide-induced β-endorphin expression and its antiallodynic effects [63]. Simultaneously, activation of GLP-1R by exenatide enhanced the expression of anti-inflammatory cytokines, including IL-10 and IL-4 [63]. The finding revealed that activation of exenatide stimulates IL-10 and β-endorphin expression through the cAMP/PKA/p38β/CREB and IL-10/IL-10R-α/STAT3 signal pathways [63] (Fig. 5A **and B**). To further elucidate the role of GLP-1R signaling during microglial activation in neuropathic pain, a comprehensive RNA-seq analysis was conducted [64]. In a similar model as above, intrathecal administration of exenatide was shown to reverse the aberrant expression of 591 genes in the spinal dorsal horn that were dysregulated by nerve injury [64]. Among the differentially expressed genes, 58 modules were identified as closely associated with microglial GLP-1R pathways and features of nerve injury, including pain hypersensitivity, ligation, paw withdrawal latency, and anxiety-related behaviors [64]. KEGG pathway analysis revealed that inflammatory signaling pathways, including those mediated by TNF-α, Toll-like receptors, and cytokine-cytokine receptor interactions, were significantly enriched in the spinal dorsal horn following nerve injury [64]. These pathways likely contribute to the neuroinflammatory state underlying neuropathic pain. Hence, intrathecal exenatide administration shifted the gene expression profile of neuropathic rats closer to that of the sham group, demonstrating its capacity to normalize the transcriptional landscape [64]. The exenatide-treated group mainly highlighted a predominant enrichment of NF-κB signaling, suggesting that

Table 3 Preclinical and clinical evidence of GLP-1RAs for treating visceral pain

Compound	Model/disease	Key findings	Ref.
***In vitro*evidence**			
Exendin-4	IEC-6 cells	Exendin-4 upregulated SERT expression via the AC/PKA signaling pathway	[58]
***In vivo*evidence**			
Exendin-4	Stress-induced defecation and visceral pain sensitivity in rats	Exendin-4 improved bowel dysfunction without impacting anxiety-like behaviors	[56]
Exendin-4	Intra-colonic infusion of acetic acid-induced visceral hypersensitivity in rats	Exendin-4 reduced visceral hypersensitivity by regulating SERT expression and downregulating TPH-1 expression	[57]
Liraglutide	LPS and WAS-induced visceral hypersensitivity in rats	Liraglutide blocked LPS-induced visceral allodynia via inhibiting inflammatory and attenuating gut permeability	[59]
Clinical evidence			
Exendin-4 and GLP-1	IBS	Exendin-4 and GLP-1 increased neurite length and ATP responses	[55]
ROSE-010	IBS	ROSE-010 offered rapid and effective acute pain relief	[60]
ROSE-010	IBS	Reduced GLP-1 and GLP-1R expression underlay ROSE-010's effectiveness in alleviating abdominal pain	[61]
ROSE-010	IBS	Female participants were more responsive to IBS pain relief with ROSE-010	[62]

exenatide may exert its effects by modulating key regulators of inflammation [64] (Fig. 5C). Additionally, exenatide improves recovery from spinal cord injury (SCI) by shifting the polarization of macrophages infiltrating into the injured spinal cord to the anti-inflammatory M2 phenotype [65]. In a rat contusion model of SCI, exenatide administration significantly elevated the expression of M2-associated markers, including Arginase 1, CD163, and CD206, on day 3 post-injury [65]. While exenatide reduced the expression of M1-associated markers (iNOS, CD86, and CD16), immunohistochemical analysis showed no significant reduction in the overall number of M1-profile cells compared to controls [65]. They also found that treatment with exenatide resulted in a marked increase in anti-inflammatory cytokines (IL-4 and IL-10) alongside a reduction in pro-inflammatory cytokines (TNFα and IL-1β) [65]. Exenatide may also mitigate SCI through alternative mechanisms, including the attenuation of ER stress [66]. In a rat moderate contusive SCI model, subcutaneous administration of exenatide immediately post-injury and again at 7 days significantly improved hindlimb motor function without inducing hypoglycemia [66]. Studies in mechanisms showed that exenatide treatment influenced the expression of key markers associated with ER stress [66]. As mentioned in the study, administration of exenatide after SCI suppressed C/EBP homologous transcription factor protein (CHOP, a pro-apoptotic transcription factor central to ER stress-mediated apoptosis) while upregulating glucose regulatory protein 78 (GRP78, an ER chaperone with cytoprotective effects) in the injured spinal cord, leading to a significant decrease in tissue damage and a significant increase in oligodendrocyte progenitor cell survival [66]. These findings suggest that, in addition to its role in modulating immune responses, exenatide confers neuroprotection by alleviating ER stress, thus preserving cellular integrity and supporting functional recovery. In a recent 2025 study using large-scale proteomic analysis of serum samples from two phase 3 clinical trials, Maretty et al. demonstrated that semaglutide modulates the circulating proteome in individuals with overweight or obesity, with or without diabetes [67]. Notably, semaglutide treatment was associated with a reduction in proteins upregulated in neuropathic pain and an increase in proteins typically downregulated in such conditions, further supporting the potential therapeutic benefits of semaglutide in managing neuropathic pain [67].

GLP-1RAs also have beneficial effects on pain-related behaviors. In a rat model of SNL, intrathecal administration of exendin-4 significantly alleviated pain-induced hippocampal neuroinflammation and enhanced cognitive recovery [68]. Electrophysiological examinations indicated a significant reduction in paw withdrawal frequency of the left limb following exendin-4 treatment, correlating with effective pain relief [68]. In the Morris water maze test, exendin-4 treatment improved cognitive performance, evidenced by reduced escape latency and shorter times to locate the platform [68]. Immunohistochemical staining and western blot analysis revealed that SNL increased the activation of microglia and astrocytes in the dentate gyrus of the hippocampus, along with elevated expression of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, which were significantly reversed by exendin-4 treatment [68]. In a study by Zhang et al., activation of GLP-1R was shown to mitigate novel-object recognition memory dysfunction in neuropathic pain model mice by modulating the hippocampal AMPK/NF-κB signaling pathway [69] (Fig. 5D). This activation reduced neuroinflammation and restored levels of key synaptic proteins [69]. Specifically, treatment with exenatide acetate increased the ratio of *p*-AMPK-Thr172/AMPK, inhibited NF-κB p65 phosphorylation, and downregulated pro-inflammatory markers, including IL-1β and TNF-α [69]. Additionally, the treatment upregulated synaptic proteins such as PSD 95 and Arc, which are crucial for synaptic plasticity and cognitive function [69] (Fig. 5D). However, the protective effects of GLP-1R

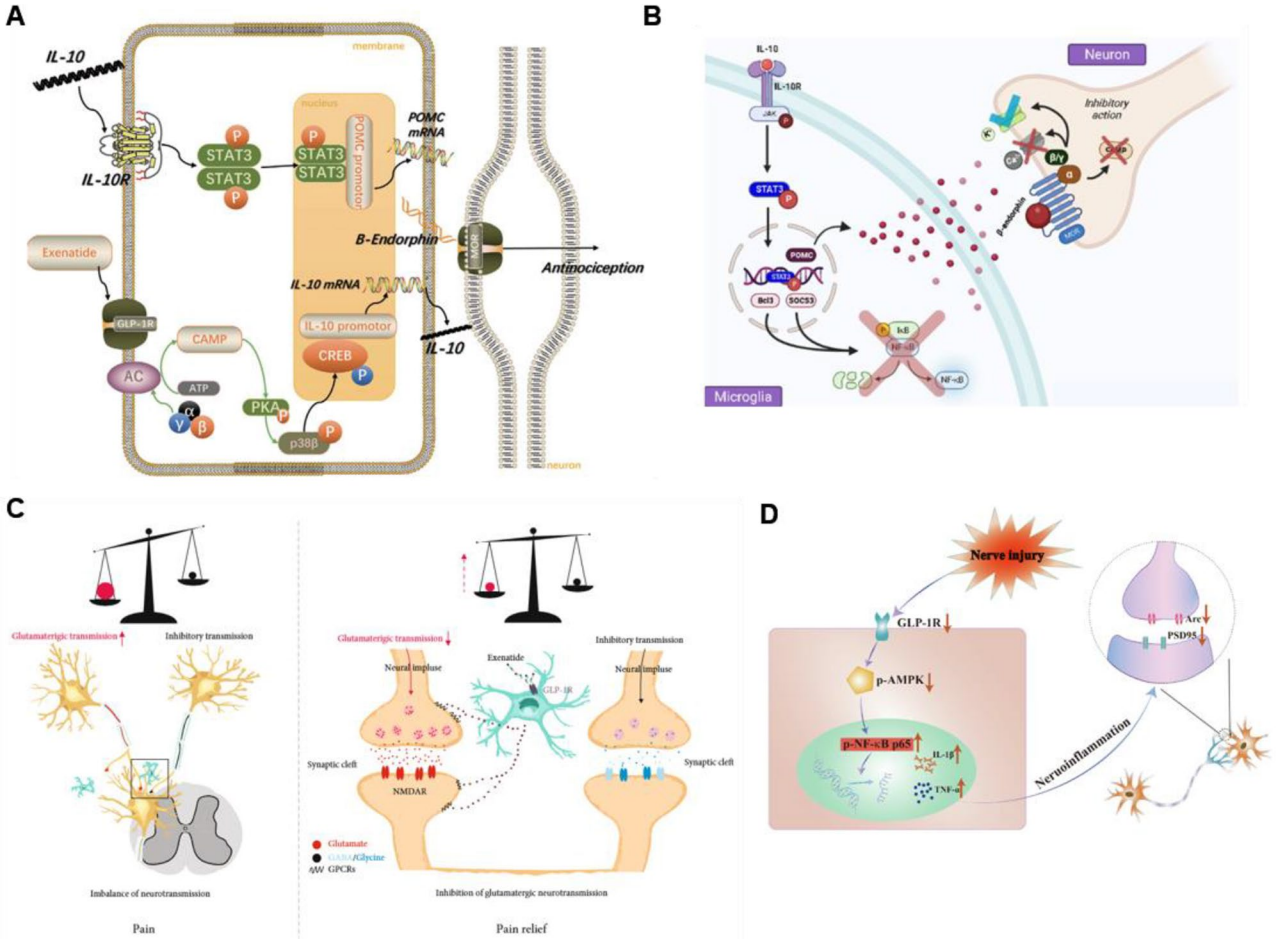

Fig. 5 (**A** and **B**) Specific stimulatory effects of exenatide on spinal microglial-β-endorphin expression and the proposed IL-10 autocrine mechanisms underlying GLP-1R activation-induced β-endorphin expression in microglia and spinal antinociception in neuropathy. Reproduced under terms of the CC-BY 4.0 licenses [75]. Copyright 2021, Frontiers Media S.A. Reproduced under terms of the CC-BY license [76]. Copyright 2023, Multidisciplinary Digital Publishing Institute. (**C**) Exenatide alleviated peripheral neuropathic pain and glutamatergic transmission and rescued 591 gene expressions associated with a spinal microglial-mediated mechanism. Reproduced under terms of the CC-BY licenses [64]. Copyright 2021, Hindawi Publishing Corporation. (**D**) Activation of GLP-1R ameliorated neuroinflammation and reversed the decreased level of synaptic proteins in mice with neuropathic pain. Reproduced with permission [69]. Copyright 2021, Elsevier. Abbreviations: IL-10: interleukin-10; IL-10R: interleukin-10 receptor; GLP-1R: glucagon-like peptide-1 receptor; AC: adenylate cyclase; ATP, adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; STAT3: signal transducer and activator of transcription 3; CREB: cAMP-response element binding protein; p38β: p38 mitogen-activated protein kinase-β; POMC: proopiomelanocortin; JAK: Janus kinase; Bcl3: b-cell lymphoma 3; SOCS3: suppressor of cytokine signaling-3; NF-κB: nuclear factor kappa-B; IκB: inhibitor of NF-κB; MOR: μ-opioid receptor; GPCRs: G-protein-coupled receptors; GABA: γ-aminobutyric acid; NMDAR: N-methyl-D-aspartic acid receptor; p-AMPK: phosphorylated AMP-activated protein kinase; p-NF-κB: phosphorylated NF-κB; IL-1β: interleukin-1β; TNF-α: tumor necrosis factor-α; Arc: activity-regulated cytoskeleton-associated protein; PSD95: postsynaptic density protein-95.

activation on memory were negated by the administration of exendin (9–39) and Compound C dihydrochloride (an AMPK inhibitor) [69].

Teneligliptin, a DPP-4 inhibitor, demonstrated mild antinociceptive effects against heat-induced acute pain, but remarkable analgesic effects against partial sciatic nerve transection (PSNT)-induced neuropathic pain in rats [70]. Furthermore, co-injection of exendin (9–39) with teneligliptin partially reversed allodynia, but not tail-flick latency, suggesting GLP-1R-independent mechanisms [70]. Immunofluorescence examination of the spinal cord revealed that teneligliptin inhibited the immunoreactivity of glial fibrillary acidic protein, indicating that its analgesic effects are associated with the suppression of spinal astrocyte activation thereby preventing neuroinflammation [70].

Lamiophlomis rotata (*L. rotata*), a widely used Tibetan medicinal herb with well-documented analgesic properties, is frequently prescribed in China for pain management. Zhu et al. found that the principal effective ingredients of *L. rotate*, shanzhiside methylester (SM) and 8-O-acetyl-SM, function as a small-molecule GLP-1R agonist, producing antinociceptive properties through activation of GLP-1Rs in a rat model of peripheral nerve

injury [71]. Subsequently, the team further found that intrathecal administration of SM has demonstrated potent, dose-dependent, and long-lasting anti-allodynic effects in neuropathic pain models induced by spinal nerve injury [72]. Notably, prolonged treatment with SM or exenatide over seven days did not result in self-tolerance to anti-allodynia or cross-tolerance to morphine or β-endorphin [72]. Conversely, morphine and β-endorphin induced both self-tolerance and cross-tolerance to SM and exenatide [72]. Mechanistically, SM significantly enhanced β-endorphin expression in the spinal dorsal horn and primary microglia [72]. This effect was fully suppressed by the microglial inhibitor minocycline and the p38 mitogen-activated protein kinase (MAPK) inhibitor SB203580, underscoring the essential role of microglial activation and the p38 MAPK pathway [72]. Furthermore, both SM and exenatide selectively activated p38 MAPK phosphorylation in the spinal cord, providing additional evidence that SM exerts its anti-allodynic effects by targeting spinal GLP-1R and promoting microglial β-endorphin synthesis via the p38 MAPK signaling cascade [72]. Morroniside, an iridoid glycoside derived from the medicinal herb *Cornus officinalis*, is a potent orthosteric agonist of GLP-1R with significant anti-hypersensitivity effects. In a rat model of neuropathic pain induced by tight ligation of L5/L6 spinal nerves, morroniside, administered either orally or intrathecally, dose-dependently alleviated mechanical allodynia, with comparable maximal efficacy (E_{max}) and an effective dose 50% (ED_{50}) values of 335 mg·kg^{-1} (oral) and 7.1 μg (intrathecal) [73]. Additionally, morroniside fully reversed thermal hyperalgesia in this model [73]. Importantly, repeated daily intrathecal injections of morroniside over seven days did not result in the development of tolerance to its anti-allodynic effects [73]. Mechanistic investigations demonstrated that the anti-hypersensitivity effects of morroniside are mediated by its activation of spinal GLP-1R [73]. Pretreatment with exendin (9–39) completely blocked the anti-allodynic effects of both systemic and intrathecal morroniside administration [73]. Further analysis revealed that morroniside's therapeutic effects are reliant on the spinal microglial expression of IL-10 and subsequent β-endorphin production [74]. Specifically, inhibiting or depleting spinal microglia abolished the anti-allodynic effects of morroniside, while neutralizing IL-10 or β-endorphin with targeted antibodies, or blocking the μ-opioid receptor, fully reversed morroniside-induced mechanical anti-allodynia [74]. At the molecular level, morroniside upregulated the gene expression of IL-10 and β-endorphin in the spinal cord of neuropathic rats as well as in primary cultured microglia [74]. Pretreatment with IL-10-neutralizing antibodies blocked morroniside-induced β-endorphin expression both in vivo and in vitro [74]. However, β-endorphin-neutralizing antibodies did not affect morroniside-induced IL-10 expression, indicating that IL-10 acts upstream of β-endorphin in this signaling cascade [74]. The findings demonstrate that morroniside alleviates neuropathic pain by activating GLP-1R and modulating spinal microglial function, leading to IL-10-mediated β-endorphin production and subsequent activation of μ-opioid receptors [74]. A brief description of this section is listed in Table 4.

Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is a prevalent and debilitating complication of diabetes mellitus, arising from neuronal damage caused by prolonged hyperglycemia. Patients with DPN frequently experience symmetric sensory disturbances, typically presenting as pain, tingling, and prickling sensations and negative symptoms such as numbness [77]. Such manifestations significantly impair quality of life, often associated with psychological comorbidities such as anxiety and depression [78]. GLP-1RAs have multifaceted biological functional properties, positioning them as a potential therapeutic option for DPN. In vitro studies demonstrated that treatment with liraglutide or exendin-4 significantly attenuated oxidative stress and cellular apoptosis in SH-SY5Y cells exposed to methylglyoxal or high glucose, which mimicked the pathophysiological conditions of diabetic neuropathy [79, 80]. Additionally, exendin-4 treatment mitigated high glucose-induced mitochondrial dysfunction, as evidenced by reduced expression levels of mitochondrial function-associated genes mitochondrial calcium uniporter (MCU) and uncoupling protein 3 (UCP3), as well as the mitochondrial fission-related gene dynamin-related protein 1 (DRP1) [79].

Simultaneously, evidence from animal models supports the beneficial effects of GLP-1RAs on DPN. In a study involving streptozotocin (STZ)-induced diabetic rats, treatment with exenatide did not significantly affect blood sugar levels, insulin levels, or the thermal response latencies of the paws. However, it did significantly reduce the decrease in motor nerve conduction velocity and paw intraepidermal fiber density observed in diabetic mice through the activation of extracellular signal-regulated kinase (ERK) signaling [81]. Another study has also reported, arginine-rich exendin-4 demonstrated efficacy in STZ-induced diabetic rats by reducing the severity of tactile allodynia [82]. This effect was achieved by reversing myelin damage and ameliorating degenerative changes in the sciatic nerve of diabetic rats [82]. Liraglutide therapy significantly mitigated DPN by enhancing motor and sensory nerve conduction velocities and restoring myelin fiber density in diabetic mice [11]. It reduced pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), chemokines, adhesion molecules and oxidative

Table 4 Preclinical evidence of GLP-1RAs for treating neuropathic pain

Compound	Model	Key findings	Ref.
***In vivo*evidence**			
Exenatide	SNL-induced neuropathic pain in rats	Microglial IL-10 mediated β-endorphin expression after GLP-1R activation through the autocrine cAMP/PKA/p38β/CREB and subsequent IL-10 receptor/STAT3 signaling pathway	[63]
Exenatide	SNL-induced neuropathic pain in rats	Activation of spinal microglial GLP-1R ameliorated inflammatory responses through gene expression and structural changes	[64]
Exenatide	SCI-induced pain in rats	Exenatide shifted the polarization of macrophages from M1 to M2 profiles	[65]
Exenatide	SCI-induced pain in rats	Exenatide decreased ER stress and hindlimb function	[66]
Exendin-4	SNL-induced neuropathic pain in rats	Exendin-4 alleviated neuroinflammatory and promote the recovery of cognitive function via GLP-1R pathway	[68]
Exendin-4	Spared nerve injury-induced neuropathic pain in mice	Exendin-4 improved recognition memory impairment via suppressing the AMPK/NF-κB pathway, and increased synaptic protein expression	[69]
Teneligliptin	PSNT-induced neuropathic pain in rats	Teneligliptin showed mild antinociceptive effects for acute pain and significant analgesic effects against neuropathic pain	[70]
SM and 8-O-acetyl-SM	SNL-induced neuropathic pain in rats	SM and 8-O-acetyl-SM were orthosteric, reversible, and intrinsic agonists of GLP-1R	[71]
SM	SNL-induced neuropathic pain in rats	SM reduced neuropathic pain by activating spinal GLP-1R and subsequently stimulating microglial β-endorphin expression via the p38 MAPK signaling pathway	[72]
Morningside	SNL-induced neuropathic pain in rats	Morroniside was an orthosteric agonist of GLP-1R and alleviated neuropathic pain by activation of spinal GLP-1R	[73]
Morroniside	SNL-induced neuropathic pain in rats	Morroniside alleviated neuropathic pain through spinal microglial IL-10 and β-endorphin expression	[74]
Clinical evidence			
Semaglutide	Participants with overweight or obesity	Semaglutide modulated protein expression related to neuropathic pain, reducing typically upregulated proteins and increasing typically downregulated ones	[67]

Abbreviations: SNL: spinal nerve ligation; SCI: spinal cord injury; PSNT: partial sciatic nerve transection; SM: shanzhiside methylester, IL-10: interleukin-10; GLP-1R: glucagon-like peptide-1 receptor; GLP-1R: glucagon-like peptide-1 receptor; PKA: protein kinase A; CREB: cAMP-response element binding protein; p38β: p38 mitogen-activated protein kinase-β; STAT3: signal transducer and activator of transcription 3; ER: endoplasmic reticulum; AMPK: AMP-activated protein kinase; NF-κB: nuclear factor kappa-B

stress, while upregulating the expression of neurotrophic factors (neuritin and NGF) [11]. Mechanistically, liraglutide significantly suppressed p38 MAPK/NFκB signaling pathways in the sciatic nerves of diabetic rats [11]. Additionally, liraglutide improved nociceptive thresholds and reversed histopathological damage of the sciatic nerve in diabetic rats induced by nicotinamide and streptozotocin [11]. Mechanistically, liraglutide normalized oxidative stress, including malondialdehyde and NO, while reduced pro-inflammatory mediators such as IL-6 and COX-2 [12]. Furthermore, liraglutide suppressed DNA fragmentation and the activity of matrix metalloproteinases-2 (MMP-2) and −9(MMP-9), while upregulating superoxide dismutase and IL-10 in the sciatic nerve [12]. Another study found that liraglutide alleviated thermal and mechanical allodynia through suppression of brain microglia NOD-like receptor protein 3 (NLRP3) inflammasome activation in diabetic rats [83]. However, the analgesic effects of liraglutide were not observed in GSK3β (S9A) mice, indicating that liraglutide relieved diabetic pain by suppressing the NLRP3 inflammasome in microglia through GSK3β [84]. Additionally, liraglutide alleviated antinociceptive behavior in the formalin test by reducing oxidative stress and inflammation in diabetic mice [30]. Interestingly, oral administration of proniosomes loaded with amitriptyline and liraglutide showed synergistic benefits for controlling blood glucose levels, alleviated pain, reduced oxidative stress and inflammation, and improved sciatic nerve histology in diabetic rats [85]. Recently, Lee et al. found that semaglutide significantly reduced DPN-associated pain behaviors and neuroinflammation in STZ-induced diabetic rats [86]. Semaglutide decreased spinal cord microglial and astrocyte activation and reduced pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and advanced glycation end products (AGEs) [86]. Although semaglutide had limited effects on hyperglycemia and weight loss, it improved lipid profiles and reduced oxidative stress [86]. PKF275-055, an analog of vildagliptin, is a novel, selective, orally bioavailable, and long-acting DPP-4 inhibitor that has

shown promising benefits in the prevention, protection, and treatment of diabetic neuropathy. PKF275-055 treatment restored mechanical sensitivity thresholds by approximately 50% and progressively improved the alteration in thermal responsiveness in diabetic rats, which was possibly mediated by counteracting the alterations in Na^+/K^+-ATPase activity and nerve conduction velocity [87].

Clinical research further reinforces the beneficial effects of GLP-1RAs on DPN. In individuals with T2DM undergoing intensive glycemic control, exenatide treatment significantly increased nerve regeneration and improved the severity of pain [88]. Another clinical study showed participants with DPN underwent nerve ultrasonography, neuropathy symptom scoring, and nerve conduction studies before and after one month of GLP-1RA therapy (semaglutide or dulaglutide) [89]. Results revealed significant reductions in tibial nerve cross-sectional area (CSA), an indicator of nerve swelling, with 86% of participants exhibiting reduced CSA and 32% achieving normal nerve morphology [89]. Improvements in neuropathy severity scores and sensory nerve conduction were observed, and follow-up at three months indicated sustained reductions in nerve CSA and enhanced clinical outcomes. These benefits appeared independent of changes in glycated haemoglobin (HbA1c) or BMI, suggesting a direct neuroprotective effect of GLP-1RAs [89]. Collectively, GLP-1-RAs are involved in the regulation of DNP mainly through the suppression of matrix remodeling, inflammation, oxidative stress, and mitochondrial dysfunction, as well as the improvement of neural structure and function [90–93] (Fig. 6). A brief description of this section is listed in Table 5.

Headache

Headaches are a heterogeneous group of conditions characterized by intermittent or persistent pain, often described as pulsating or pressure-like. Among these, migraine and intracranial hypertension are prominent underlying causes. In a nitroglycerin-induced chronic migraine (CM) mouse model, GLP-1R expression was markedly increased and colocalized with microglia and astrocytes in the trigeminal nucleus caudalis (TNC) [94]. Treatment with liraglutide effectively alleviated central sensitization associated with CM [94] (Fig. 7A). Mechanistically, liraglutide administration inhibited the upregulation of pain-related markers in the TNC, including calcitonin gene-related peptide (CGRP), c-fos, and

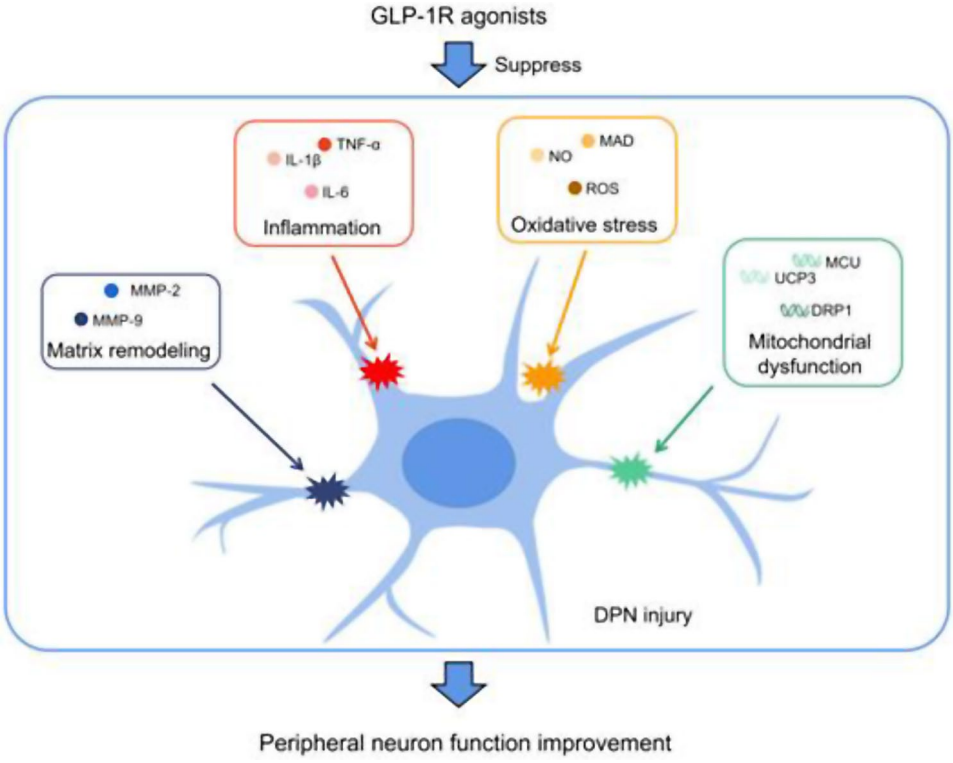

Fig. 6 GLP-1RAs improved neuron functions in DPN injury through inhibiting inflammation, oxidative stress, mitochondrial dysfunction, and matrix remodeling. Reproduced under terms of the CC-BY licenses [90]. Copyright 2024, Frontiers Media S.A. Abbreviations: GLP-1R: glucagon-like peptide-1 receptor; MMP-2: matrix metalloproteinases-2; MMP-9: matrix metalloproteinases-9; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6, MAD: malondialdehyde, NO: nitric oxide; ROS: reactive oxygen species; MCU: mitochondrial calcium uniporter; UCP3: uncoupling protein 3; DRP1: gene dynamin-related protein 1

Table 5 Preclinical and clinical evidence of GLP-1RAs for treating diabetic peripheral neuropathy

Compound	Model/disease	Key findings	Ref.
***In vitro*evidence**			
Liraglutide	Methylglyoxal-induced SH-SY5Y cells	Liraglutide reduced oxidative stress and improved energy metabolism	[80]
Exendin-4	High glucose-induced SH-SY5Y cells	Exendin-4 protected against high glucose-induced mitochondrial dysfunction and oxidative stress through GLP-1R/Akt signaling pathway	[79]
***In vivo*evidence**			
Exenatide	STZ-induced diabetic rats	Exenatide attenuated the reductions of motor nerve conduction velocity and paw intraepidermal fiber density	[81]
Liraglutide	STZ-induced diabetic rats	Liraglutide prevented nerve dysfunction via p38 MAPK/NFκB signaling pathways, independent of glycemic control	[11]
Liraglutide	Nicotinamide and STZ-induced diabetic rats	Liraglutide improved animal behavior and inhibited inflammation, oxidative stress and extracellular matrix remodeling	[12]
Liraglutide	STZ-induced diabetic rats	Intracerebroventricular administration of liraglutide alleviated thermal and mechanical allodynia	[83]
Liraglutide	STZ-induced diabetic mice	GSK3β contributed to liraglutide's analgesic effect via microglial NLRP3 inflammasome	[84]
Liraglutide	STZ-induced diabetic mice	Liraglutide alleviated diabetic pain by reducing inflammatory and oxidative stress	[30]
Liraglutide	STZ-induced diabetic rats	Liraglutide-loaded proniosomes inhibited oxidative stress and inflammation, and improved sciatic nerve structure	[85]
Arginine-rich exenatide	STZ-induced diabetic rats	Arginine-rich exenatide increased myelin basic protein expression and improved neurological function	[82]
Semaglutide	STZ-induced diabetic rats	Semaglutide alleviated diabetic pain by inhibiting inflammation and oxidative stress	[86]
Exendin-4	STZ-induced diabetic rats	Exendin-4 prevented peripheral nerve degeneration via antiapoptotic effects and restoration of cAMP content	[92]
PKF275-055	STZ-induced diabetic rats	PKF275-055 restored mechanical sensitivity thresholds by about 50% and gradually improved thermal responsiveness	[87]
Clinical evidence			
Exenatide	T2DM	Exenatide improved corneal nerve regeneration	[88]
Dulaglutide and Semaglutide	T2DM	GLP-1 RAs reduced the severity of neuropathy and improved neural structure and function	[89]

components of the PI3K/Akt signaling pathway [94]. Additionally, liraglutide reduced microglial activation in the TNC, as evidenced by decreased Iba-1 expression and reduced levels of pro-inflammatory cytokines IL-1β and TNF-α [94]. It also mitigated morphological changes in microglia, such as process retraction [94]. In vitro experiments using LPS-stimulated BV-2 microglia confirmed that liraglutide decreased the protein levels of IL-1β and TNF-α [94]. Another study demonstrated that liraglutide alleviated CM-associated hyperalgesia by inhibiting CGRP, phosphorylated ERK (*p*-ERK), and c-fos protein levels in the TNC, with a concurrent increase in IL-10 release [95] (Fig. 7B).

Elevated intracranial pressure (ICP), often associated with headaches, has been linked to cerebrospinal fluid (CSF) secretion regulation by the GLP-1R, expressed in the human and rodent choroid plexus [96]. Exendin-4 demonstrated a GLP-1R-mediated reduction in ICP in a rodent model of hydrocephalus by inhibiting Na^+- and K^+-dependent adenosine triphosphatase activity in the choroid plexus [97]. This suggests that GLP-1R agonists could be repurposed for treating ICP-related headaches. An open-label, single-center, case-control pilot study investigated the effects of GLP-1RAs in individuals with idiopathic intracranial hypertension (IIH) and obesity (BMI ≥ 30 kg/m²) [98] (Fig. 7C). The intervention group ($n = 13$) received semaglutide or liraglutide alongside standard body weight management, while the control group ($n = 26$) underwent standard weight management alone [98]. After six months, participants in the GLP-1RA-treated group achieved significantly greater weight loss compared to the control group [98]. This weight reduction was accompanied by fewer headache days and a decreased requirement for acetazolamide [98]. A randomized, placebo-controlled trial further evaluated the effect of exenatide on ICP in women with IIH [99]. Exenatide significantly reduced ICP at 2.5 h, 24 h, and 12 weeks compared to placebo, with no significant weight loss observed in the exenatide group [99]. This indicates a direct effect of exenatide on ICP modulation, likely mediated by its action at the choroid plexus [99]. Additionally, mean monthly headache days were significantly reduced in the exenatide group compared to placebo, further supporting its therapeutic potential [99]. Cognitive function, often impaired in conditions with raised ICP such as IIH, was not adversely affected by exenatide treatment

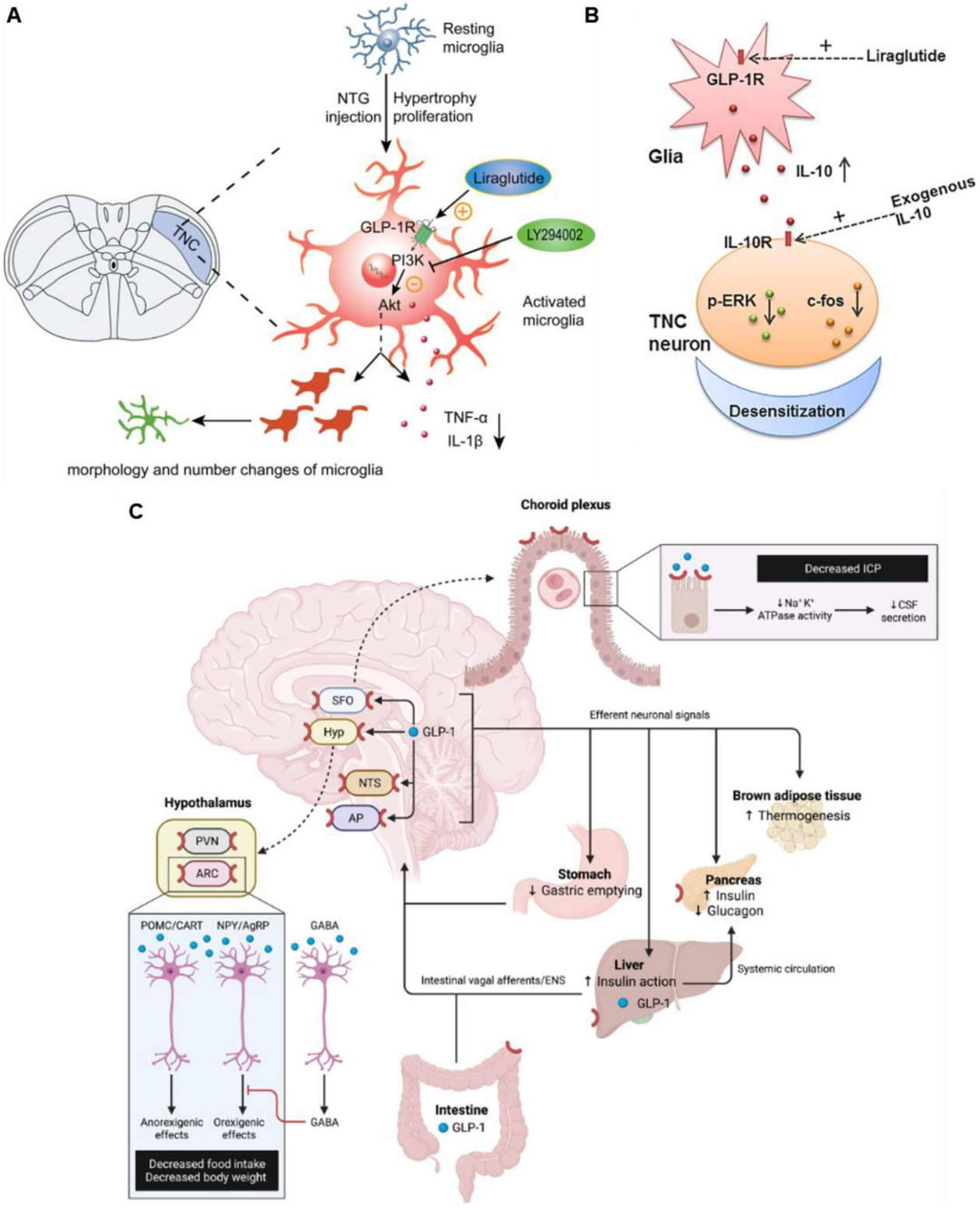

Fig. 7 (See legend on next page.)

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Fig. 7 (**A**) Liraglutide treatment inhibited microglial cell proliferation, morphological changes, and inflammatory cytokine expression through PI3K/Akt pathway in the CM mice. Reproduced under terms of the CC-BY 4.0 license [94]. Copyright 2021, Springer Nature. (**B**) Liraglutide activated glial GLP-1R and promoted the release of IL-10 in the TNC in the CM mice. Reproduced with permission [95]. Copyright 2023, Elsevier. (**C**) GLP-1, secreted from gut, reached at choroid plexus to reduce Na^+/K^+ ATPase activity, leading to decreased CSF secretion and consequently decreased ICP. Reproduced under terms of the CC-BY 4.0 license [98]. Copyright 2023, Springer Nature. Abbreviations: GLP-1R: glucagon-like peptide-1 receptor; TNC: trigeminal nucleus caudalis; NTG: nitroglycerin; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-10: interleukin-10; IL-10R: interleukin-10 receptor; p-ERK: phosphorylated ERK; GLP-1: glucagon-like peptide-1; SFO: subfornical organ; Hyp: hypothalamus; NTS: nucleus tractus solitarii; AP: area postrema; PVN: paraventricular nucleus; ARC: arcuate nucleus; POMC: proopiomelanocortin; CART: cocaine- and amphetamine-regulated transcript; NPY: neuropeptide Y; AgRP: agouti-related peptide; GABA: γ-aminobutyric acid; ICP: intracranial pressure; CSF: cerebrospinal fluid.

in an exploratory study of women with IIH over 12 weeks [100]. However, abrupt discontinuation of GLP-1R agonists in patients with metabolic disorders may lead to rapid weight regain and potential exacerbation of IIH symptoms, as reported in a case study [101]. A brief description of this section is listed in Table 6.

Cancer pain

Gong et al. found that intrathecal exenatide effectively and reversibly blocked bone cancer-induced mechanical allodynia in ipsilateral paws, with the peak effect at 0.5 h and a duration longer than 4 h in rat models of bone cancer pain [24]. Importantly, exenatide did not significantly alter withdrawal thresholds in contralateral paws [24]. The anti-hypersensitive effects were completely prevented by GLP-1R antagonism and GLP-1R gene knockdown [24]. Mechanistic investigations revealed that exenatide stimulated β-endorphin release from both spinal cord tissue and cultured primary microglia [24]. The antiallodynic effect was entirely blocked by the microglial inhibitor minocycline, β-endorphin antiserum, or the opioid receptor antagonist naloxone [24]. The findings highlight the spinal microglial GLP-1R/β-endorphin pathway involved in the modulating of pain hypersensitivity induced by bone cancer [24]. In a similar model, Zhu et al. found that intragastric administration of *L. rotata* aqueous extract (30, 100, 300, 1,000, and 3,000 mg/kg) produced dose-dependent reductions in mechanical allodynia in ipsilateral paws without significantly affecting contralateral paw thresholds [71]. The antiallodynic effect was long-lasting, with a peak effect at 1 h post-gavage and a duration exceeding 4 h [71]. The dose-response analysis determined an ED_{50} of 242.9 mg/kg and a maximum efficacy (E_{max}) of 54%, based on 1-h post-administration values [71]. A brief description of this section is listed in Table 7.

Discussion

The current review explores the evolving role of GLP-1RAs in the management of various pain conditions, beyond their traditional application in metabolic diseases. As versatile therapeutic agents, GLP-1RAs demonstrated their benefits across a range of pain syndromes, including inflammatory nociception, visceral hypersensitivity, neuropathic pain, diabetic peripheral neuropathy (DPN), cancer pain and headaches (Fig. 1). In inflammatory pain circumstances, preclinical studies demonstrate robust anti-inflammatory and antinociceptive effects via spinal β-endorphin release and microglial modulation [24, 31]. Non-peptide agonists like geniposide show oral bioavailability, broadening therapeutic potential [33]. However, clinical trials remain limited, with no human trials specifically targeting inflammatory pain. In osteoarthritis conditions, preclinical models highlight direct anti-catabolic and immunomodulatory actions (e.g., liraglutide reduces IL-6, MMP-3) [45]. However, human studies showed that improvements in pain are predominantly attributed to weight loss, rather than direct analgesic effects in the condition of osteoarthritis [47]. Future clinical trials should refine the investigation of the direct analgesic properties of GLP-1RAs in osteoarthritis, differentiating these from the benefits linked to weight reduction, to better evaluate their clinical utility in managing osteoarthritis-related pain.

GLP-1RAs show promise in regulating the intestinal nervous system, immune system, and endocrine pathways, offering therapeutic potential for conditions such as IBS [55–57, 59]. Notably, ROSE-010 displayed a gender difference in treatment response, with female patients showing a more favorable response in terms of pain relief [62]. This underscores the need for gender-specific approaches in clinical practice, optimizing the therapeutic efficacy of GLP-1 analogs based on patient characteristics and symptomatology. Besides, the efficacy is inconsistent across IBS subtypes, with ad hoc minimal relief in diarrhea-predominant IBS [62].

Preclinical evidence supports the role of GLP-1RAs in alleviating neuropathic pain through the modulation of microglial activity, inflammatory cytokine production and β-endorphin release [63, 65, 68, 70–74]. GLP-1RAs also inhibited inflammatory signaling, contributing to their analgesic efficacy in neuropathic pain, particularly in chronic pain [64, 69]. Especially, their analgesic effects are achieved without the development of tolerance, offering a significant advantage over traditional pain management strategies. Nevertheless, clinical validation is sparse, with only proteomic data indirectly supporting mechanisms [67]. Also, human trials targeting neuropathic pain are absent.

Table 6 Preclinical and clinical evidence of GLP-1RAs for treating headache

Compound	Model/disease	Key findings	Ref.
***In vivo*evidence**			
Liraglutide	Nitroglycerin-induced chronic migraine in mice	Liraglutide suppressed the central sensitization by inhibiting microglial activation via the PI3K/Akt pathway	[94]
Liraglutide	Nitroglycerin-induced chronic migraine in mice	Liraglutide alleviated the central sensitization by stimulating the release of IL-10	[95]
Exendin-4	Rat model of hydrocephalus	Exendin-4 reduced raised intracranial pressure through inhibiting Na^+/ K^+ATPase activity	[97]
Clinical evidence			
Semaglutide and liraglutide	IIH	GLP-1-RAs promoted weight loss and reduced headaches, allowing for lower acetazolamide doses	[98]
Exenatide	IIH	Exenatide significantly and meaningfully lowered intracranial pressure	[99]
Exenatide	IIH	Exenatide improved cognitive function in IIH	[100]
Duraglutide	IIH	The patient stopped duraglutide abruptly regained the weight lost within a month and subsequently developed IIH	[101]

Table 7 Preclinical evidence of GLP-1RAs for treating cancer pain

Compound	Model	Key findings	Ref.
Exenatide	Bone cancer-induced pain in rats	Exenatide promoted β-endorphin release	[24]
L. rotata	Bone cancer-induced pain in rats	SM and 8-O-acetyl-SM were the effective ingredients for anti-hyperalgesia	[71]

Additionally, GLP-1RAs ameliorate DPN through various mechanisms, including the inhibition of inflammation, oxidative stress, and extracellular matrix remodeling, while simultaneously improving neural structure, function, and energy metabolism [11, 12, 30, 79–86]. There are differences in the efficacy and mechanisms of different GLP-1RAs in the treatment of DPN. For example, liraglutide has been shown to improve neural function through multiple signaling pathways, whereas semaglutide appears to exert more pronounced effects on neuroinflammation and neural tissue remodeling [11, 84, 86]. Regretfully, variability exists among analogs, complicating protocol standardization. Hence, individualized treatment strategies, considering factors such as patient age, underlying comorbidities, and DPN severity, will be critical for optimizing therapeutic outcomes.

GLP-1RAs have been found to modulate the pathogenesis and progression of migraine by attenuating neuroinflammation and suppressing neuronal hyperactivity [94, 95]. GLP-1RAs also reduce intracranial pressure and alleviate headache symptoms associated with conditions like idiopathic intracranial hypertension, particularly in female patients [98–101]. Notably, exenatide has demonstrated the ability to reduce intracranial pressure without significant changes in body weight, presenting a novel therapeutic approach for managing headaches linked to intracranial hypertension [99]. It is worth noting that, abrupt discontinuation poses a risk of ICP rebound and symptom exacerbation [101], while the cognitive safety associated with chronic use remains underexplored [100].

GLP-1RAs show significant potential as a novel class of drugs for managing cancer pain. Preclinical evidence shows spinal GLP-1R activation attenuates bone cancer-induced allodynia via β-endorphin release [24]. However, no clinical trials validate efficacy in humans. In addition, integration with existing cancer therapies, including surgery, radiotherapy, and targeted therapies remain unstudied. Clinical trials are also essential to evaluate the safety, tolerability, and potential synergistic effects of GLP-1RAs in the context of cancer pain management. Such studies will help clarify their role and feasibility in comprehensive pain management and establish the potential for GLP-1RAs as an integral part of therapeutic protocols for cancer-related pain.

Limitations

Despite the promising analgesic potential of GLP-1RAs, several challenges remain before their widespread application. Evidence supporting their analgesic effects comes from animal models, which may not fully reflect human studies. Clinical validation is sparse, particularly for cancer pain and neuropathic pain. In osteoarthritis, pain relief is often attributed to weight loss rather than direct analgesic effects, complicating the evaluation of GLP-1RAs' efficacy. Similarly, in IBS, treatments like ROSE-010 show varying efficacy depending on gender, which limits generalizability and underscores the need for more personalized therapeutic approaches. While GLP-1RAs are known to affect pathways like β-endorphin release and anti-inflammation, the precise mechanisms underlying their analgesic effects across different pain modalities are still not fully understood. Additionally, as seen in IIH, the abrupt discontinuation of GLP-1RAs may lead to symptom exacerbation, raising concerns about potential dependency. Additionally, in obesity-associated conditions such as OA and headaches, distinguishing the direct analgesic effects of GLP-1RAs from the secondary benefits of weight reduction remains a methodological challenge. Moreover, despite the encouraging preclinical data, rigorous phase III trials are necessary to confirm

the safety, tolerability, and specificity of GLP-1RAs in pain management.

In addition, as a narrative review, we synthesize the existing literature thematically, rather than relying on systematic meta-analysis. This approach enables a broad exploration of mechanisms and clinical implications, but it also introduces the potential for selection bias. Regarding the inclusion of preprints, its inclusion was carefully justified to reflect cutting-edge developments, and we emphasize that its preliminary nature does not detract from the overall evidence base.

Conclusion and perspective

Emerging preclinical evidence suggests that GLP-1 receptor agonists (GLP-1RAs) may represent a novel class of therapeutics for pain management. While initial clinical observations indicate promising effects in specific conditions such as diabetic peripheral neuropathy, irritable bowel syndrome, and idiopathic intracranial hypertension, rigorous clinical trials are needed to confirm their efficacy, elucidate weight-loss-independent mechanisms, and establish comprehensive safety profiles across various pain conditions. Currently, many GLP-1RAs have already been approved for the treatment of diabetes and obesity and could be repurposed for the treatment of pain symptoms. Their repurposing aligns with precision medicine paradigms, enabling tailored therapies for patients with comorbid conditions like obesity, diabetes, and chronic pain. However, their translation to clinical practice hinges on addressing critical gaps, including the need for rigorous human trials, long-term safety assessments, and mechanistic clarity. Future research should prioritize the development of next-generation agonists, explore combination therapies, and integrate precision medicine approaches to optimize patient outcomes. By bridging these gaps, GLP-1RAs could herald a new era in pain management, offering hope for patients with refractory or complex pain conditions.

Abbreviations

GLP-1RAs	Glucagon-like peptide-1 receptor agonists
T2DM	Type 2 diabetes mellitus
DPP-4	Dipeptidyl peptidase IV
GLP-1R	Glucagon-like peptide-1 receptor
cAMP	Cyclic adenosine monophosphate
PKA	Protein kinase A
PI3K	Phosphatidylinositol 3-kinase
Akt	Protein kinase B
AD	Alzheimer's diseases
TRPV1	Transient receptor potential vanilloid 1
OA	Osteoarthritis
KOA	Knee OA
MIA	Monoiodoacetate
IL-6	Interleukin 6
PGE2	Prostaglandin E2
NO	Nitric oxide
ER	Endoplasmic reticulum
IL-1β	Interleukin-1β
MMP-3	Matrix metalloproteinases-3
MMP-13	Matrix metalloproteinases-13
ROS	Reactive oxygen species
BMI	Body mass index
IBS	Irritable bowel syndrome
ATP	Adenosine triphosphate
SERT	Serotonin transporter
TPH-1	Tryptophan hydroxylase-1
AC	Adenylate cyclase
LPS	Lipopolysaccharide
WAS	Water avoidance stress
IBS-C	Constipation-predominant IBS
SNL	Spinal nerve ligation
SCI	Spinal cord injury
CHOP	C/EBP homologous transcription factor protein
GRP78	Glucose regulatory protein 78
PSNT	Partial sciatic nerve transection
L. rotate	Lamiophlomis rotate
SM	Shanzhiside methylester
MAPK	p38 mitogen-activated protein kinase
DPN	Diabetic peripheral neuropathy
MCU	Mitochondrial calcium uniporter
UCP3	Uncoupling protein 3
DRP1	Dynamin-related protein 1
STZ	Streptozotocin
ERK	Extracellular signal-regulated kinase
MMP-2	Matrix metalloproteinases-2
MMP-9	Matrix metalloproteinases-9
NLRP3	NOD-like receptor protein 3
AGEs	Advanced glycation end products
CSA	Cross-sectional area
CM	Chronic migraine
TNC	Trigeminal nucleus caudalis
CGRP	Calcitonin gene-related peptide
ICP	Intracranial pressure
CSF	Cerebrospinal fluid
IIH	Idiopathic intracranial hypertension

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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