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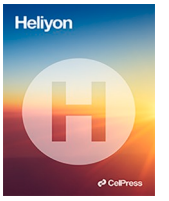

Review article

The role of orphan G protein-coupled receptors in pain

Chengfei Xu [a], Yahui Wang [b], Huadong Ni [c], Ming Yao [c], Liang Cheng [a,**], Xuewu Lin [b,*]

[a] Department of Anesthesiology, The Third People's Hospital of Bengbu, Bengbu, 233000, PR China
[b] Department of Anesthesiology, The First Affiliated Hospital of Bengbu Medical University, Bengbu, 233000, PR China
[c] Department of Anesthesiology and Pain Research Center, Affiliated Hospital of Jiaxing University, Jiaxing, 314000, PR China

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ABSTRACT

G protein-coupled receptors (GPCRs), which form the largest family of membrane protein receptors in humans, are highly complex signaling systems with intricate structures and dynamic conformations and locations. Among these receptors, a specific subset is referred to as orphan GPCRs (oGPCRs) and has garnered significant interest in pain research due to their role in both central and peripheral nervous system function. The diversity of GPCR functions is attributed to multiple factors, including allosteric modulators, signaling bias, oligomerization, constitutive signaling, and compartmentalized signaling. This review primarily focuses on the recent advances in oGPCR research on pain mechanisms, discussing the role of specific oGPCRs including GPR34, GPR37, GPR65, GPR83, GPR84, GPR85, GPR132, GPR151, GPR160, GPR171, GPR177, and GPR183. The orphan receptors among these receptors associated with central nervous system diseases are also briefly described. Understanding the functions of these oGPCRs can contribute not only to a deeper understanding of pain mechanisms but also offer a reference for discovering new targets for pain treatment.

1. Introduction

In the year 2020, The International Association for the Study of Pain (IASP) took the initiative to redefine the concept of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or an experience similar to it" [1]. This statement highlights the multidimensional aspects of pain perception and provides a better understanding of the subjective nature of pain. The activation of primary sensory neurons, located in the dorsal root or trigeminal ganglia, is the initial response to a noxious stimulus, whether physical or chemical. These neurons transmit pain signals to the secondary neurons situated in the dorsal horn of the spinal cord [2]. Following this, the processing and transmission of pain signals occur contralaterally to diverse regions of the brain center for information integration and subsequent modulation. The transmission of downstream fibers facilitates either the inhibition or facilitation of the injurious sensation [3]. The mechanisms of peripheral and central sensitization are the regulatory factors in the onset of nociceptive sensitization, which are executed by primary and secondary sensory neurons, respectively [4]. The complex and intricate processes that govern pain perception and modulation underline the multifactorial and dynamic nature of pain. A deeper understanding of these mechanisms will help to develop effective therapeutic strategies to alleviate pain and improve the quality of life

* Corresponding author.
** Corresponding author.
E-mail addresses: bbchengliang@163.com (L. Cheng), pain2009@126.com (X. Lin).

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for people suffering from pain (see Fig. 1).

G protein-coupled receptors (GPCRs) are an extensive group of human membrane protein receptors, comprising a variety of classes, such as the rhodopsin-like receptors (class A), secretin receptor family (class B), metabotropic glutamate (class C), cAMP receptors (class E) and Frizzled/Smoothened receptors (class F) [5]. These receptors are highly expressed in the central nervous system (CNS), with up to 90% of GPCR-encoding genes in the human genome being expressed in this context, where they play a critical role in regulating injurious signaling in the neurons of the upstream and downstream pain pathways [6,7]. FDA has approved over 475 drugs targeting GPCRs, accounting for 34% of all approved drugs, with a staggering 41 approvals in just the last 5 years [8]. Nevertheless, identifying new drug targets is becoming increasingly critical as the available receptor target space is nearing saturation [8]. Opioid receptors, which are a type of GPCR, are the primary drug target for clinical analgesia, but their long-term use in chronic pain management is limited by an array of adverse effects, including respiratory depression, pruritus, and addiction [9]. As such, it is crucial to explore alternative drug targets to address the unmet need for safe and effective pain management.

The ubiquitous and critical family of cell membrane proteins known as GPCRs serve as paramount mediators of signal transduction across the membrane. GPCRs demonstrate an impressive capacity to activate downstream signaling pathways by triggering Gα subunit dissociation from Gβγ subunit upon ligand binding [10,11]. This activation leads to recruitment of a plethora of effectors, such as adenylyl cyclase, phospholipase C, or ion channels. It is worth noting, however, that despite their potential as drug targets, clinical efficacy of GPCRs has been limited. This is due, in part, to our incomplete understanding of the complex signaling pathways that GPCRs facilitate, particularly with respect to ligand-specific responses [8,12]. Indeed, the complexity of GPCRs arises from their highly intricate structure, which includes a staggering 17 α subunits, 5 β subunits, and 12 γ subunits [13]. However, the functional diversity of GPCRs is not solely attributable to structural components. Factors such as conformational regulation, signaling bias, oligomerization, constitutive signaling, and compartmentalized signaling also contribute to the remarkable diversity of GPCR signaling [14,15].

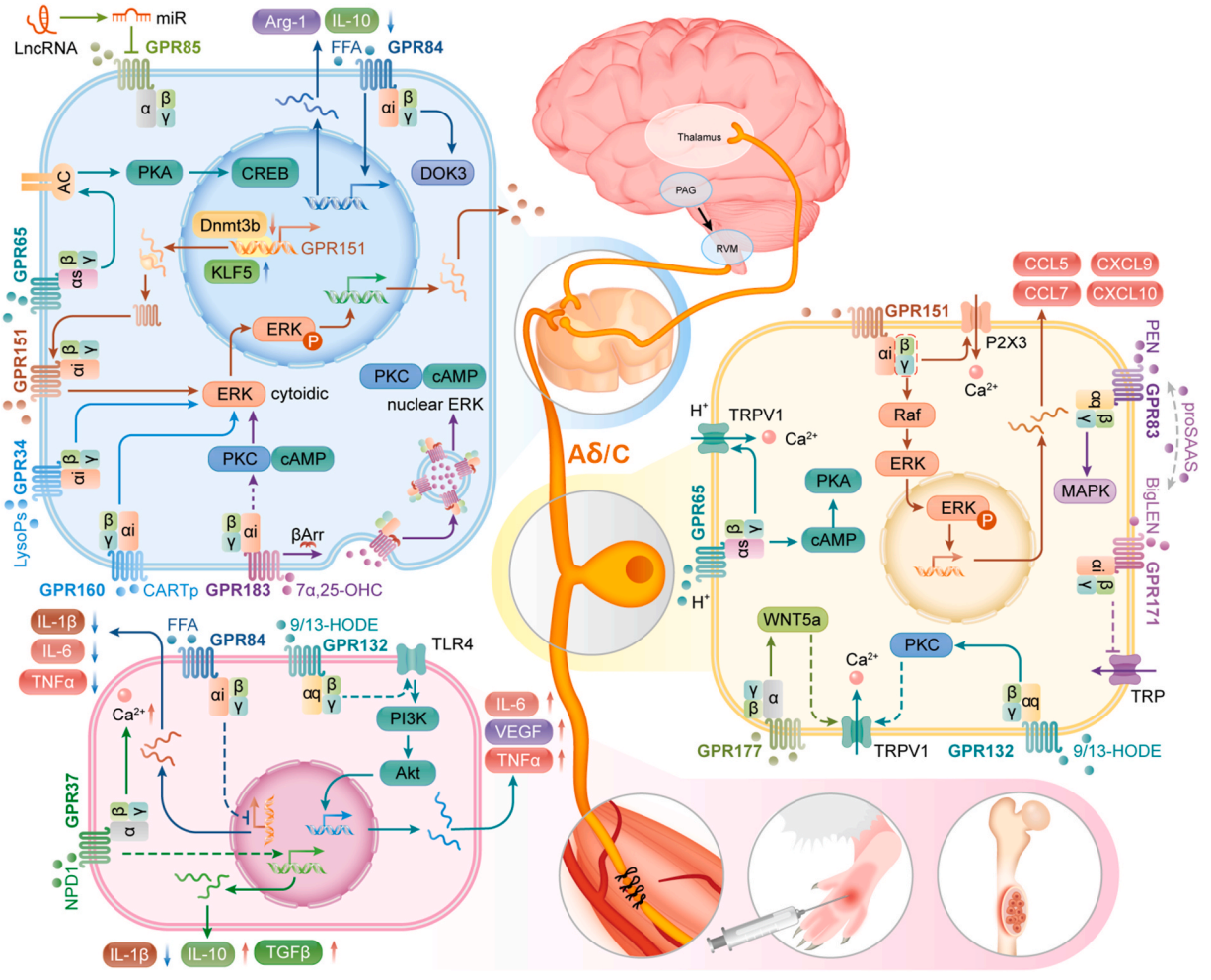

Fig. 1. The role of orphan GPCRs in pain signaling. Dorsal root ganglion (DRG) neurons collect pain signals originating from the peripheral nervous system, which are then conveyed through A-delta and C-fibers to the dorsal horn of the spinal cord. Subsequently, these signals ascend to the brain where they are perceived and subjected to processing. This figure offers a summary of recent research discoveries regarding the role of orphan receptors in regulating pain at the peripheral nerve endings, DRG, and dorsal horn of the spinal cord.

Table 1
An overview on the effects of the orphan GPCRs in the modulation of pain and analgesia.

Receptor	Models	Gender/ Species	Endogenous ligands or agonist	G protein type	Distribution	The role in pain	References
GPR34	SNI	Male/ mice	LysoPS	Gαi	spinal cord	GPR34 is mainly expressed in microglia and GPR34-KO significantly reduces the release of inflammatory factors, leading to pain relief.	[31]
GPR37	Zymosan capsaicin	Male/ mice	ARU, NPD1, TX14, prosaposin, Saposin C, osteocalcin, and chlorogenic acid		Macrophage	Macrophages express GPR37, which contributes to inflammation relief. NPD1 and TX14 bind to GPR37, eliciting a GPR37-mediated Ca^{2+} increase in macrophages.	[33] [34]
GPR65	Carrageenan CFA	Female/ Male mice		Gαs	DRG Spinal cord	GPR65 knockdown diminishes CFA-induced inflammatory pain, accompanied by a reduction in calcium influx upon GPR65 inhibition.	[35]
	BCP	Female/ rat				GPR65 activates PKA and is implicated in BCP. Intrathecal administration of siRNA provides mechanical pain relief.	[36]
GPR83	CFA/CIPN	Male/ mice	PEN		DRG	GPR83 knockdown alleviates mechanical pain sensitivity. Pain relief is achieved with pEN, despite its effect of reducing both thermal and mechanical thresholds.	[37]
GPR84	CCI	Male/ mice	FFA, 6-OAU	Gαi	Spinal cord macrophage	GPR84 triggers microglial inflammation through DOK3, and its knockout results in reduced mechanical pain.	[38]
	PNL	Female/ Male mice				GPR84 modulates macrophages to participate in inflammation. Knockdown of GPR84 mitigates PNL-induced mechanical and thermal pain thresholds.	[39] [40]
GPR85	BCP	Female			Spinal cord	BCP upregulates GPR85 expression in spinal dorsal horn neurons. Inhibition of GPR85 by miR143 alleviates mechanical pain sensitivity in rats.	[41]
GPR132	SNI	Male/ mice	9-HODE, 13-HODE	Gαq	Macrophages	Knockout of GPR132 diminishes SNI-induced mechanical pain sensitivity and substantially diminishes the secretion of TNFα, IL-6, and VEGF.	[42]
	CIPN				DRG	GPR132 participates in CIPN by activating TRPV1 via PKC. Knockout of GPR132 relieves 9-HODE-induced mechanical pain sensitivity.	[43]
GPR151	SNI	Male/ mice			DRG	GPR151 gene mutations have no effect on SNI-induced mechanical pain sensitivity.	[44]
	CCI				DRG	GPR151 is predominantly present in non-peptidergic C-fiber DRG neurons. Conditional knockout of Gpr151 mitigates neuropathic pain mediated by P2X3.	[19]
	pIONT				TG	GPR151 binds to Gαi proteins and subsequent activates ERK via Gβγ to participate in pIONT. GPR151 knockout reduces the release of inflammatory molecules.	[45]
	SNL				Spinal cord	The demethylation of the GPR151 promoter region facilitates the binding of the transcription factor KLF5, leading to an upregulation of GPR151 expression, which is implicated in SNL.	[46]
GPR160	CCI/SNI/SNL	Female/ Male rat	CARTp	Gαi	Spinal cord	Elevated GPR160 expression in the dorsal horn of the spinal cord is involved in neuropathic pain through the ERK signaling pathway. The mechanical pain may be relieved by intrathecal injection of siRNA.	[47]
GPR171	CFA/CCI/ PINP	Male/ mice	BigLEN	Gαi	DRG	GPR171, coupled to Gαi, modulates noxious ion channels to weaken pain signaling.	[48]

(*continued on next page*)

Table 1 (*continued*)

Receptor	Models	Gender/ Species	Endogenous ligands or agonist	G protein type	Distribution	The role in pain	References
	CFA/CIPN	Female/ Male mice			PAG	MS15203 (i.p.) demonstrated analgesic effects in male mice, but not in their female counterparts.	[49]
GPR177	CCI	Female/ Male mice			DRG	GPR177 is predominantly expressed in class A neurons with large diameters in the dorsal root ganglion and plays a role in synaptic transmission and plasticity modulation.	[18]
GPR183	Neuropathic pain	Female/ Male mice	7α,25-OHC	Gαi	Spinal cord	GPR183, primarily expressed on astrocytes and coupled to Gαi, mediates pain signaling. Upon 7a,25-OHC activation, GPR183 recruits β-arrestin 2 and undergoes internalization.	[50]
	CCI					7a,25-OHC/GPR183 activates MAPK and NFκB signaling pathways to mediate inflammation. SAE-14 can inhibit these effects.	[51]

Moreover, recent research has shown that the conventional understanding of GPCR internalization as leading to receptor desensitization and signal termination is incomplete. In reality, internalization of GPCRs can actually result in activation, and the signaling that occurs within the internalized membrane system can be more sustained than that which occurs within the plasma membrane [16]. During internalization, GPCRs activate multiple signaling pathways, leading to complex and diverse physiological responses that are still not fully understood. Given the remarkable potential of GPCRs as drug targets, it is increasingly pressing that we conduct further research to elucidate the intricacies of GPCR signaling mechanisms and identify more effective targets for therapeutic interventions.

Orphan G protein-coupled receptors (oGPCRs) represent a specific subset of GPCRs that still elude the identification of their endogenous ligands [5]. While there has been considerable advancement in the structural and pharmacological research of GPCRs, the characterization of oGPCRs remains somewhat limited, and therefore rather perplexing. Nevertheless, it is worthwhile to note that oGPCRs play a multitude of diverse roles in the central nervous system, offering tantalizing new prospects for drug discovery as a prospective reservoir of drug targets [17]. Furthermore, oGPCRs have surfaced as major players in the study of pain mechanisms, with their vital roles in both central and peripheral sensitization being firmly established [18,19]. As a consequence, we present here a staged format summary of the most recent discoveries on these distinct oGPCRs (GPR34, GPR37, GPR65, GPR83, GPR84, GPR85, GPR132, GPR151, GPR160, GPR171, GPR177 and GPR183), that play a role in pain mechanisms.

2. oGPCRs and pain

GPR34, belonging to the rhodopsin-like family [20], was initially discovered back in the 1990s by two completely independent research groups [21,22]. Later studies conducted by Sugo et al. revealed the existence of lyso-phosphatidylserine (lyso-PS) as an endogenous ligand of GPR34 [23]. Table 1 shows an overview on the effects of the orphan GPCRs in the modulation of pain and analgesia. This lyso-PS, which results from the enzymatic hydrolysis of membrane phosphatidylserine (PS), manages to elicit mast cell degranulation and is susceptible to pertussis toxin (a Gαi inhibitor) activation of the ERK signaling pathway. Perhaps more fascinatingly, Yang et al. found that lyso-PS plays a critical role in stimulating gastric cancer metastasis through the activation of downstream signaling via GPR34/Gαi [24]. Interestingly, GPR34 activation has also been demonstrated to enhance the transcription of genes that are responsible for causing pain [25,26], through the activation of ERK [27], PI3K/Akt [28], and NF-κB [29]. (S)-3-(4-(benzyloxy) phenyl)-2-(2-phenoxyacetamido) propanoic acid was identified as a new class of GPR34 antagonists [30]. It was able to dose-dependently inhibit lysophosphatidylserine-induced ERK1/2 phosphorylation in CHO cells expressing GPR34. For example, Sayo et al. discovered that GPR34 mRNA expression was significantly increased in microglia in the dorsal horn of the spinal cord in a mouse model of neuropathic pain [31]. In addition, they found that intrathecal injection of GPR34 antagonists helped to alleviate painful behavior, indicating that GPR34 may be involved in pain by inducing pro-inflammatory factor expression in microglia [31]. It's worth noting that GPR34 knockout mice exhibited impaired immune function and altered microglial morphology, as additional studies have found. These studies found reduced microglial phagocytic activity and elevated tumor necrosis factor (TNF)-α release in *Gpr34*$^{-/-}$ mice [32].

GPR37, also known as the Parkin-related endothelin-like receptor (Pael-R) [52], was first cloned in 1997 and has been found to be predominantly expressed in the CNS, including regions such as the amygdala, basal ganglia, hippocampus, frontal cortex, and hypothalamus, and notably, exhibits exceptionally high expression in the spinal cord [53]. Neuroprotectin D1 (NPD1), a novel pro-repair lipid small molecule with potent anti-inflammatory effects, as an endogenous ligand for GPR37 [54], has generated immense interest in the scientific community. Indeed, activation of GPR37 by NPD1 binding induces increased Ca^{2+} signaling and phagocytosis in macrophages, while also providing relief from inflammatory pain [33,34]. Notably, PRLMs have been shown to play a crucial role in the regulation of acute and chronic pain through their diverse effects on neurons, immune cells and the nervous system [55,56]. The study by Bang et al. has also shown that GPR37 expressed from macrophages, but not microglia [33]. Macrophages exist in different

phenotypes, including pro-inflammatory M1 and anti-inflammatory M2 phenotypes [57,58], and GPR37 is a key regulator of macrophage phenotypes. Macrophages expressing GPR37 exhibit an anti-inflammatory M2 phenotype, producing lower levels of IL-1β and higher levels of IL-10 and TGFβ, suggesting that GPR37 is an important mediator of inflammation and immune regulation [54]. In a model of inflammatory pain, *GPR37*$^{-/-}$ mice exhibited prolonged thermal and mechanical nociceptive hyperalgesia, similar to the effects of IL-1β injections. This highlights the importance of GPR37 in alleviating inflammatory pain [54]. In addition, targeting GPR37 may lead to novel therapeutics for the treatment of inflammation, infection and neurological diseases [59].

GPR65, also known as TDAG8, a proton-sensing G protein-coupled receptor belonging to the Ovarian Cancer G protein-coupled Receptor 1 (OGR1) family, a clan inclusive of GPR65, GPR4, OGR1, and GPR132 [60,61]. These receptors, with their 40–50% homology, utilize extracellular histidine residues to sense protons and fully activated at a pH of 6.4–6.8 [62–64], and activates adenylate cyclase (AC) via Gαs protein coupling [65]. The OGR1 family finds expression in the dorsal root ganglion (DRG) of spinal nerves, with most receptors (a whopping 75–82%) distributed among small-diameter neurons sensitive to injury, with more than half of them residing in IB4-positive neurons [66]. Next, scholars have inquired into the expression and function of GPR65 in pain models, finding that GPR65 expression in the DRG of the ipsilateral L4-6 segment increased significantly (1.4–1.9fold) when carrageenan was injected 24 h after plantar injection, remaining high 72 h after injection. On the other hand, expression significantly increased (2.5–4.3 fold) at 24 h after CFA injection, only to be reduced (1.2–1.6 fold) 72 h after injection [67]. In the inflammatory pain model (CFA), activation of GPR65 sensitized TRPV1 to capsaicin, and in the presence of GPR65, protons enhanced TRPV1-mediated Ca^{2+} inward flow, ultimately causing nociceptive hyperalgesia. As such, GPR65 performs an important role in inflammatory pain [35]. Dai et al. uncovered that GPR65 expression in the spinal cord increased over time in a rat bone cancer pain (BCP) model, and continuous intrathecal injection of GPR65 siRNA relieved spontaneous and mechanical pain [36]. It was then further demonstrated that GPR65 is involved in the pathogenesis of BCP through activation of the PKA signaling pathway.

GPR83, also known as GPR72, JP05, or GIR, belongs to the rhodopsin-like family [68] and is highly expressed in the human brain. Its gene is located on human chromosome 11q21 [69] and encodes a 423 amino acid protein of approximately 48 KDa [70]. PEN, a neuropeptide produced by the proSAAS precursor protein [71], is thought to be an endogenous ligand for GPR83 [72]. The PEN/GPR83 system is involved in food intake and body weight regulation, as well as in drug addiction and reward disorders [73]. In addition to PEN, proSAAS also produces other neuropeptides, such as SAAS, PEN, and LEN, of which BigLEN is an endogenous ligand for GPR171 [71,74]. The PEN/GPR83 and BigLEN/GPR171 systems may interact in controlling feeding and rewarding behavior [72]. Studies have shown that the GPR83 gene is involved in regulating pain sensitivity. Kim et al. found that neurons lacking the GPR83 gene had a notable reduction in the number and peak of capsaicin-responsive neurons [37]. In a CFA-induced inflammatory pain model, knockdown of GPR83 significantly lowered mechanical pain and thermal nociceptive sensitization. Similarly, in a paclitaxel-induced CIPN model, knockdown of GPR83 reduced mechanical pain and cold pain behavior in mice. These findings suggest that GPR83 plays a crucial role in pain regulation [37].

GPR84, also referred to as EX33, belongs to the rhodopsin-like or family A of GPCRs [75] and acts as a receptor that mediates signaling through coupling with Gαi/o proteins [40]. This receptor is predominantly expressed in the peripheral immune cells and microglia of the nervous system, and its expression is upregulated following appropriate immune stimulation, such as exposure to lipopolysaccharide or TNF [40,76]. Endogenous ligands for GPR84 are believed to be free fatty acids with intermediate carbon chain length C9–C14 [40]. Wei L et al. used endogenous, natural and surrogate agonists for GPR84 and found that 6-*n*-octylaminouracil (6-OAU), embelin and capric acid rapidly induced membrane ruffling and motility in cultured microglia, but failed to promote microglial pro-inflammatory cytokine expression [77]. The role of GPR84 in regulating Th1 differentiation to promote inflammatory responses has been established. Bouchard et al. demonstrated that GPR84 mRNA expression in cortical and spinal microglia was significantly upregulated in models of endotoxaemia and autoimmune encephalomyelitis, indicating a potential role for GPR84 in immune regulation and neuroinflammation [76,78]. In a mouse model of partial sciatic nerve injury (PNL), GPR84 mRNA expression was found to be significantly increased in the sciatic nerve and spinal cord [39]. Furthermore, greater upregulation was observed in the sciatic nerve of WT mice compared to the spinal cord, suggesting that GPR84-mediated signaling may be more important in peripheral pathogenesis. Nicol et al. reported that GPR84 knockout mice did not exhibit mechanical or thermal pain sensitization 21 days after nerve injury. Moreover, transcription of the anti-inflammatory macrophage marker Arg-1 and cytokine IL-10 was significantly upregulated in the nerves of GPR84 knockout mice. Additionally, Gao et al. found that DOK3 protein, in association with GPR84, is involved in neuropathic pain [38]. Taken together, these findings suggest that GPR84 plays a critical role in immune regulation and pain modulation in both the central and peripheral nervous systems. In addition, GPR84 signaling is thought to play an important role in the pathogenesis of osteoarthritis (OA), and GPR84 activation or supplementation with medium-chain FFAs has the potential to prevent the onset and progression of OA [79].

GPR85, also referred to as SREB2, is a member of the Super conserved receptor expressed in brain (SREB) family, which comprises receptors that are exclusively expressed in neurons. SREB family members are SREB1 (GPR27), SREB2 (GPR85) and SREB3 (GPR173) [80]. The primary amino acid sequence of GPR85 is fully conserved in humans and mice, and the gene is located on human chromosome 7q31 [81]. GPR85 is notably expressed during the initial stages of neuronal differentiation in the central nervous system and is associated with hippocampal neuromodulation of learning and memory [82,83]. In the context of bone cancer pain (BCP), GPR85 has been demonstrated to play a vital role. In a study by Ni et al., it was found that both mRNA and protein expression of GPR85 were significantly increased in the dorsal horn of the spinal cord in a rat model of BCP and were mainly expressed on neurons [41]. Further studies showed that injection of AAV-*Gpr85*-shRNA in the dorsal horn of the spinal cord reduced mechanical pain sensitivity in rats. The expression of GPR85 was regulated by miR-143-5p. These findings suggest that GPR85 could be a valuable target for the development of innovative treatments for chronic pain.

GPR132, also known as G2A, is a member of the OGR1 family of receptors expressed in 32% of dorsal root ganglia (DRG) neurons

and co-localized with TRPV1 in 46% of GPR132-positive neurons [66]. However, compared to other members of the OGR1 family, GPR132 exhibits the weakest response to acidic stimuli [84,85]. It is believed that 9-hydroxyoctadecadienoic acid (9-HODE), an oxidized linoleic acid metabolite, is an endogenous ligand for GPR132, and its activation occurs in a concentration-dependent manner. Upon activation, GPR132 sensitizes TRPV1 by activating Gαq and protein kinase C (PKC) [86,87]. Hohmann et al. further demonstrated that 9-HODE induced TRPV1 sensitization in a concentration-dependent manner and that cells pretreated with 9-HODE displayed significantly increased capsaicin-induced inward currents [43]. Although 13-HODE is also a GPR132 ligand, it requires a concentration approximately 6-fold higher than that of 9-HODE to activate GPR132. In a chemotherapy-induced peripheral neuropathic pain model (CIPN), GPR132 knockout mice showed significantly reduced foot reduction latencies, indicating that 9-HODE contributes to sensory neuron TRPV1 sensitization via GPR132 activation of PKC involved in CIPN [43]. Additionally, in a preserved nerve injury (SNI) model, Osthues et al. found that GPR132 knockout mice exhibited significantly reduced mechanical hypersensitivity and significantly lower concentrations of IL-6 and TNFα in the ipsilateral sciatic nerve [42]. These results suggest that GPR132 plays a critical role in pain modulation and inflammation in the peripheral nervous system.

GPR151, also known as PGR7, GALR4, GPCR-2037, or GALRL, belongs to the rhodopsin-like family and is encoded by a gene located at 5q32 [88]. Although there are currently no known ligands for GPR151, Gpr151 mRNA expression is significantly upregulated in the medial and lateral regions of the brain [89,90], which are known to play key roles in pain, stress, memory, and depression [91]. Notably, GPR151 expression is also upregulated in models of CCI-induced neuropathic pain [92,93] and burn-induced pain [94], suggesting a potential role for GPR151 in pain modulation. Jiang et al. reported that in a pIONT-induced trigeminal neuralgia model, GPR151 is expressed in TG neurons, particularly in those that are NF200-positive [45]. Activation of GPR151 by coupling with Gαi proteins leads to downstream activation of the ERK pathway, resulting in neuronal excitation and upregulation of chemokine expression in sensory neurons, contributing to the pathogenesis of trigeminal neuralgia. In addition, demethylation of CpG islands in the promoter region of GPR151 leads to increased binding to the transcription factor KLF5, which activates the MAPK pathway that is involved in pain in a model of SNL [46]. Xia et al. observed that GPR151 is primarily expressed in the DRG non-peptidergic neuron IB4 and is coupled to the P2X3 ion channel, which induces inward Ca^{2+} currents and increases neuronal excitability, ultimately modulating P2X3 ion channel and microglial activity and contributing to neuropathic pain in a model of CCI [19]. However, Holmes et al. found no statistically significant differences in pain thresholds in GPR151 MUT mice following an SNI model [44]. Overall, the mechanisms underlying the function of GPR151 in different species and pain models remain incompletely understood and require further investigation.

GPR160 is an abundantly expressed and highly conserved protein within the central nervous system of both humans and rodents, specifically in neurons, astrocytes, and microglia [95–97]. It is located on human chromosome 3q26 [98] and has been identified as a binding site for the endogenous ligand cocaine- and amphetamine-regulated transcript (CARTp) [47]. The biological activity of CARTp varies among species, with humans and rats producing distinct biologically active forms [99]. GPR160 and CARTp are implicated in reward, addiction, anorexia, and depression [100,101]. Pertussis toxin, a Gαi subunit inhibitor, has been shown to attenuate the reward experience mediated by CARTp, and U0126, an ERK inhibitor, has been shown to attenuate the CARTp-induced increase in CREB mRNA. Additionally, in a rat chronic constrictive model, GPR160 expression was significantly increased in the dorsal horn of the spinal cord, and intrathecal injection of GPR160 siRNA or GPR160 Ab relieved mechanical pain and cold pain [47].

GPR171, also known as H963, is an orphan receptor that shares homology with the P2Y receptor [102] and is linked to the Gαi/o protein, which inhibits cAMP production [103]. The endogenous ligand for GPR171 is believed to be bigLEN, derived from the neuropeptide precursor ProSAAS, which is a widely expressed in the brain and involved in numerous functions [104]. ProSAAS expression is elevated in the cerebrospinal fluid and periaqueductal grey matter of the midbrain in patients with fibromyalgia [105,106]. Wardman et al. have demonstrated that administering a GPR171 antagonist in the basolateral amygdala reduces anxiety-like behavior in mice [107], while McDermott et al. have found that GPR171 is present in a subpopulation of GABA neurons in the periaqueductal grey matter, and activation of GPR171 mediates anti-harm sensation by stimulating output neurons in the medulla oblongata [108]. Cho et al. conducted a study using CFA, CCI and postoperative incisional pain models to investigate the efficacy of intrathecal injections of GPR171 agonists (bigLEN and MS15203) in alleviating pain, potentially through the inhibition of transient receptor potential (TRP) ion channels [48]. Results indicated that both agonists were effective in reducing pain. Furthermore, the study revealed that more than 50% of GPR171 positive neurons expressed CGRP and over 30% of GPR171 positive neurons expressed IB4 in the DRG. Additionally, the study investigated the role of GPR171 in chronic neuropathic and inflammatory pain in male and female mice. Sequential intraperitoneal injections of MS15203 significantly reduced pain duration in male mice, but no similar effects were observed in female mice. Ram et al. have found that CIPN induces a decrease in GPR171 protein levels in vlPAG of male mice, which is restored after MS15203 treatment [49]. The increase in ProSAAS endogenous ligands in the cerebrospinal fluid of neuropathic pain patients may represent an adaptation to this condition and restore GPR171 signaling because of the reduced expression of GPR171 receptors in the brain of neuropathic pain patients [105].

GPR177, also known as Wntless, Wls, Evi or Srt, is located at 1p31.3 [109] and plays a crucial role in regulating the synthesis, assembly, and secretion of nearly all Wnt ligands [110,111]. Single-cell RNA sequencing analysis has revealed that GPR177 is predominantly expressed in class A DRG neurons [112], and further research by Korkut and Liao et al. has demonstrated its critical role in regulating *trans*-synaptic signaling and synaptic plasticity [113,114]. Xie et al. have found that GPR177 is selectively expressed in large-diameter class A primary sensory neurons, mainly co-localized with NF200, and is a key molecule in promoting diabetic neuropathic pain (DNP) [18]. Specifically, GPR177 activates TRPV1 ion channels through Wnt5a, leading to fast inward currents, and selectively activates small-diameter class C DRGs in a TRPV1-dependent manner. The activation of small-diameter class C DRG injurious sensory neurons by GPR177 results in the development of neuropathic pain.

GPR183, also known as EBI2, is a member of the rhodopsin-like family initially cloned in the late 20th century [115]. GPR183 has

been proposed to act as a chemotactic receptor with a crucial role in B-cell maturation, and its endogenous ligand has been identified as the oxysterol 7a,25-dihydroxycholesterol (7a,25-OHC) [116,117]. The receptor has a similar expression pattern in rodents [118], with the human receptor sequence showing 88% homology to the rodent sequence, as determined by National Center for Biotechnology Information (NCBI) Blast comparison [119]. Recent studies have indicated that GPR183 is expressed in astrocytes in the central nervous system [120], and microglia can produce and release 7a,25-OHC [121]. Activation of GPR183 by 7a,25-OHC results in coupling to Gai proteins [51], which leads to the inhibition of AC activity, an increase in phosphorylation of ERK and p38, and triggers serum response element (SRE) activity [116,117,122,123]. Braden et al. found that Gpr183 expression was significantly upregulated in the dorsal horn of the spinal cord in rats after CCI, while intrathecal injection of antagonists reversed pain hypersensitivity [50]. Raithel et al. found that GPR183 expression was also upregulated in the spinal cord in a postoperative pain model in rats, further suggesting a correlation between GPR183 and pain [124]. Recent advances have revealed that "internalization activation" of GPCRs provides a novel understanding of GPCR signaling, as it enables rapid and efficient signal delivery [16]. Upon activation by 7a,25-OHC, GPR183 is internalized by recruiting β-arrestin 2, which is then transported to the late endosome and Golgi before being recycled back to the plasma membrane [125]. β-arrestin 2 is a scaffolding protein that regulates the internalization and desensitization of GPCRs and mediates G protein non-dependent signaling, including MAPK and NF-κB signaling pathways [126].

3. oGPCRs and CNS diseases

Orphan receptors encompass a diverse range of physiological functions in vivo, rendering their pharmacological modulation a potential therapeutic avenue for a variety of diseases, including neuropsychiatric and neurodegenerative disorders. The present study focuses on the characterization of several orphan receptors, such as GPR37, GPR171, and GPR85, and their putative roles in the pathogenesis of Parkinson's disease, anxiety-related behaviors, autism, and schizophrenia, respectively [17]. Specifically, GPR37 has been observed to aggregate in the substantia nigra of some Parkinson's disease patients and interact with HSPA1A, Parkin, and prosaposin [127,128]. GPR37 has been implicated in a spectrum of consequential neurological conditions, encompassing Parkinson's disease (PD), inflammatory processes, nociceptive responses, and autism spectrum disorders [129]. GPR171, on the other hand, has been demonstrated to regulate anxiety-like behavior and contextual fear conditioning via the BigLEN-GPR171 peptide receptor system within the basolateral amygdala (BLA). Notably, neuropeptide-receptor systems in the BLA have been shown to be critical for anxiety and mood disorders [130]. Finally, GPR85 has been found to be highly expressed in the hippocampal dentate gyrus of both rodents and humans, suggesting its potential involvement in the pathogenesis of schizophrenia [83,131].

4. Conclusion

GPCRs are the most prominent drug targets in the pharmaceutical industry. Nevertheless, approximately 75% of these receptors remain unexplored for therapeutic purposes. Small molecule drugs or peptides are typical drug candidates that target GPCRs. However, they may exhibit off-target toxicity due to their high lipophilicity and molecular weight [132]. Therapeutic monoclonal antibodies (mAbs) targeting GPCRs have emerged as advantageous candidates due to their high target specificity, favorable pharmacokinetics, dosing frequency, and blood-brain barrier penetration [133]. The pharmacokinetic stability and low immunogenicity of mAbs have also made them suitable for integration in various forms such as antibody fragments, bispecific, multi-specific formats, and antibody-drug conjugates (ADCs) [134]. Unlike small molecule drugs, mAbs can modulate GPCR signaling in several ways. They can block the binding of natural ligands to the receptor, bind to regions other than the active site (metameric modulators), spatially block orthosteric ligands from entering the binding site, bind and stabilize the inactive state of the receptor, activate the receptor by stabilizing its active signaling state in the absence of natural ligands, increase receptor signaling by stabilizing the agonist-bound state of the receptor, and alter GPCR signaling by promoting dimerization in the case of bivalent antibodies [135]. Moreover, the recent matter concerning antibody-based therapeutics for migraine, which selectively target the calcitonin gene-related peptide (CGRP) axis for the treatment or prophylaxis of migraines, exemplifies a triumphant translational journey from laboratory research to clinical application [136].

In the present article, we reviewed the most recent findings regarding the role of orphan GPCRs in the modulation of pain. Despite the identification of some ligands, further research is necessary to thoroughly comprehend their functions and affirm their therapeutic potential. Multiple oGPCRs have been identified without their corresponding ligands, which can be attributed to various factors, including assay sensitivity and validity, ligand instability, or constitutive signaling (it can self-activate in the absence of ligands) of the receptor [135]. An alternative hypothesis is that GPCRs can form functional complexes with accessory proteins, in particular receptor activity-modifying proteins (RAMPs) [137]. Recent studies indicate a broader prevalence of GPCR-RAMP interactions than originally thought [138]. In particular, pharmacological agents have been designed to selectively modulate GPCR-RAMP complexes. These revelations have significant implications for the development of GPCR-targeted drugs, and greatly enhance our understanding of GPCR pharmacology, biology and regulatory mechanisms [139]. To investigate oGPCR function, classical knockout methods, as well as chemogenetics and optogenetics techniques, are frequently employed [140]. In addition, monoclonal antibodies targeting oGPCRs may prove useful in comprehending the functions of these receptors and verifying their potential as drug targets.

5. Outlook

Existing analgesic drugs (including opioids and NSAIDs) may induce serious side effects. Therefore, development of safe and efficient painkillers has been pursued by numerous researchers. Orphan GPCRs are new candidate targets that could address the

shortcomings of previous pain treatments. Prior investigations have aimed at identifying ligands for oGPCRs and small molecules that interact with them, a process known as deorphanization, to understand their physiological roles and investigate their potential as drug targets. However, clinical trials have revealed the risks associated with small molecule compounds, including off-target effects, emphasizing the superiority of monoclonal antibodies. Monoclonal antibodies targeting oGPCRs have emerged as promising therapeutics for pain management, providing superior target specificity and reduced side effects. In recent years, machine learning models have been used to predict drug targets [141]. GPR132 and GPR109B were predicted to be G protein-coupled receptor (GPCR) genes of high priority in the context of rheumatoid arthritis [142]. Notably, oGPCRs have also been linked to the pathophysiology of CNS diseases, such as depression and anxiety [17], suggesting that targeting these receptors for pain management may offer additional benefits by alleviating psychiatric symptoms. Much effort is needed to reveal the role of orphan GPCRs in the regulation of pain.

Ethics statement

Review and approval by an ethics committee was not needed for this study because this was a literature review and no new data were collected and analyzed.

Data availability statement

This is a review article, no data was used.

CRediT authorship contribution statement

Chengfei Xu: Writing – original draft. **Yahui Wang:** Data curation. **Huadong Ni:** Data curation. **Ming Yao:** Data curation. **Liang Cheng:** Writing – review & editing. **Xuewu Lin:** Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

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