

Review

The Role of Satellite Glial Cells in Opioid Modulation and Chronic Pain: A Systematic Review

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Abstract

Satellite glial cells (SGCs) play a critical role in the development and maintenance of chronic pain through complex interactions with inflammatory mediators and the opioid pathway. This systematic review synthesizes recent advances in the molecular mechanisms underlying SGC activation and implications for chronic pain management, particularly in conditions associated with the dorsal root ganglia (DRG) and trigeminal ganglia (TG). A systematic search was conducted in four databases (PubMed, Embase, Scopus, and Web of Science) covering studies published between January 2004 and May 2026. After screening 111 records, 19 studies were included. This review highlights how pro-inflammatory cytokines such as IL-1 β , IL-1 α , and TNF- α , as well as neurotransmitters like ATP and glutamate, contribute to SGC activation, neuroinflammation, and pain modulation. It also explores the role of receptors like CXCR4, TLR4, and P2X7 in SGCs in enhancing analgesic effects and their contributions to opioid tolerance and hyperalgesia. The findings underscore the potential of targeting SGCs to improve pain management outcomes across various pain models, including neuropathic, cancer-related, and visceral pain. Despite promising insights, variability in study methodologies and the complexity of glial-neuronal interactions present challenges. Future research should focus on standardizing experimental protocols and developing targeted therapies to modulate SGC activity to offer hope for patients suffering from chronic pain, particularly in managing opioid tolerance.

Keywords: satellite glial cells; chronic pain; analgesics; opioid; opioid-related disorders; receptors; opioid; trigeminal ganglion; dorsal root ganglion



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1. Introduction

Pain is a major contributor to human suffering and remains one of the leading causes of medical consultation worldwide. It affects millions of people, leading to diminished quality of life, decreased economic productivity, and a significant strain on healthcare systems [1–3]. According to the International Association for the Study of Pain (IASP), chronic pain is defined as pain that persists or recurs for longer than three months, often

outlasting the normal healing process and becoming a distinct clinical condition [4]. Chronic pain conditions, such as neuropathic pain, diabetic neuropathy, and postherpetic neuralgia, are often refractory to conventional treatment [5]. These conditions are not only debilitating but also contribute to substantial healthcare costs and loss of productivity [6].

Recent advances in neuroscience have highlighted the critical role of satellite glial cells (SGCs) in the peripheral nervous system (PNS) in pain development and maintenance [1,7,8]. These cells, which surround the sensory neurons in the dorsal root ganglia (DRG) and trigeminal ganglia (TG), have gained attention for their involvement in pain modulation through the release of pro-inflammatory cytokines and the alteration of neuronal excitability [9]. Emerging evidence suggests that SGCs may also play a crucial role in the morphine/opioid pathway, potentially influencing opioids' efficacy and side effects [10]. This is particularly relevant for chronic pain conditions, which are associated with peripheral and central sensitization [11]. Understanding the complex interactions between SGCs and opioids offers promising avenues for developing targeted therapies that enhance pain relief while minimizing adverse effects.

Despite the growing interest in SGCs and their potential role in pain management, there remains a significant gap in the literature regarding the specific molecules involved in the morphine/opioid pathway related to SGCs and their contributions to chronic pain mechanisms. Although some studies have identified neurotransmitters, cytokines, and other molecules associated with SGC activity, the intricate web of molecular interactions and pathways underlying opioid-mediated pain modulation remains poorly understood. For instance, molecules such as ATP (adenosine triphosphate), glutamate, and pro-inflammatory cytokines have been implicated in SGC activation [12,13], but their exact roles and interactions with opioid receptors are not fully delineated. Additionally, crosstalk between SGCs and other cell types, such as microglia and macrophage-like cells, further challenges description of their role in the pain pathway [14]. This gap limits the development of targeted therapies that could modulate SGC activity and enhance the effectiveness of opioids in managing chronic pain.

This systematic review aims to analyze the current evidence on molecules associated with SGC activation and their involvement in the morphine/opioid pathway underlying chronic pain mechanisms. By integrating findings from recent studies, this review seeks to clarify the molecular interactions underlying SGC-mediated opioid response modulation and identify potential targets for developing more effective and safer analgesic therapies.

2. Methods

2.1. Study Design

This systematic review aims to synthesize current evidence on molecules associated with SGC activation and their involvement in the morphine/opioid pathway in chronic pain mechanisms. The review focuses on chronic pain conditions—specifically those linked to the DRG and TG—to provide insight into potential therapeutic targets and molecular interactions involving SGCs, and was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The complete PRISMA 2020 checklist and detailed search strategies used for each database are provided as Supplementary Materials.

2.2. Literature Search Strategy

A comprehensive literature search was conducted across multiple databases, including PubMed, Embase, Scopus, and Web of Science, to identify relevant studies published between January 2004 and May 2026. The search strategy utilized a combination of keywords related to SGCs, opioid pathways, and associated molecules. The core terms “satellite glia”

and “satellite glial cell” were selected to maximize sensitivity for this specific glial cell population, while “morphine” and “opioid” were chosen as the primary pharmacological terms to capture both mechanistic and translational studies involving opioid-related pain modulation. The last search was performed on 8 May 2026.

The search strategy was developed to address the following guiding question: “In individuals or animal models with chronic pain, which molecules associated with SGCs modulate or interact with the opioid pathway, and what role do they play in the mechanisms of opioid-induced pain modulation?”

To ensure thorough identification of the relevant literature, slightly different search strategies were employed for each database considering the specific search functionalities and indexing systems of each platform, as shown in Table 1. Additionally, reference lists of relevant review articles were manually searched to identify additional relevant studies.

Table 1. Search strategy according to the databases.

Database	Search Strategy
PubMed	(satellite glia* OR satellite glial cell*) AND (Morphine OR Opioid)
Embase	(‘satellite glia*’ OR ‘satellite glial cell*’) AND (‘morphine’ OR ‘opioid’)
Scopus	TITLE-ABS-KEY (“satellite glia*” OR “satellite glial cell*”) AND TITLE-ABS-KEY (“Morphine” OR “Opioid”)
Web of Science	TS=(“satellite glia*” OR “satellite glial cell*”) AND TS=(“Morphine” OR “Opioid”)

2.3. Inclusion and Exclusion Criteria

Studies were selected according to predefined eligibility criteria.

2.3.1. Inclusion Criteria

- Studies investigating SGC activation in relation to chronic pain mechanisms.
- Research examining the role of SGCs in the morphine/opioid pathway.
- Articles published in peer-reviewed journals between 2004 and 2026.
- Studies involving animal models, cell cultures, or human subjects related to DRG and TG.
- Articles available in English, Portuguese, or Spanish.

2.3.2. Exclusion Criteria

- Studies not directly related to SGC or chronic pain.
- Reviews, meta-analyses, editorials, and opinion pieces without original data.
- Studies focusing solely on central nervous system (CNS) glial cells.

2.4. Study Selection

All retrieved records were imported into the Rayyan platform for screening and duplicate removal. Two reviewers independently screened titles and abstracts. Discrepancies were resolved through discussion or consultation with a third reviewer. Full texts of potentially relevant studies were subsequently assessed for eligibility.

2.5. Data Extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form developed for this review. Each reviewer independently extracted data from the included studies. Any discrepancies were discussed and resolved through

consensus. When necessary, a third reviewer was consulted to resolve disagreements and ensure consistency in the extracted information.

Data were systematically extracted from each study using a structured extraction form. The extraction process focused on key categories.

Study identification included the study title, authors, publication year, DOI, and institutional affiliations. Information on the study's geographical location, original language, sources of sponsorship, trial registration numbers, and any reported conflicts of interest was also documented, as well as details regarding ethics approval and the study's primary aim.

Methodological details covered study design, including whether the research involved in vitro or in vivo models. For in vivo studies, specifics such as animal species, strain, sample size, and experimental conditions were noted. In vitro studies included details on cell types, culture conditions, and passage numbers. Interventions were thoroughly documented, focusing on the molecules studied, dosages, routes of administration, and timing and duration of exposure. Control conditions and any co-interventions applied were also recorded.

Outcome measures centered on primary and secondary outcomes relevant to SGC activation and pain modulation. This included pain-related metrics, molecular and immunological outcomes, neuroinflammatory markers, and neurophysiological changes. Methods used for outcome assessment, such as assays, imaging techniques, and statistical analyses, were also documented.

Results and conclusions were summarized to highlight key findings, including the effects of interventions on SGC pathways, neuron–glia communication, and receptor–ligand interactions. Genetic and epigenetic modifications relevant to the study objectives were also captured. Attention was given to implications for future research and limitations discussed by the authors.

2.6. Quality Assessment

Methodological quality was assessed using a modified version of the OHAT Risk of Bias Rating Tool, which applies to both human and preclinical studies [15]. The assessment considered domains such as selection bias, performance bias, detection bias, attrition bias, reporting bias, confounding bias, conflict of interest bias, and any other potential biases (*OHAT Risk of Bias Rating Tool for Human and Animal Studies*) [16]. Assessment was independently performed by two reviewers; disagreements were resolved through discussion until consensus was reached.

2.7. Certainty of Evidence Assessment

A formal assessment of the certainty of the evidence using the GRADE approach was not performed due to substantial methodological heterogeneity among the included studies and the predominance of preclinical experimental designs. Instead, the findings were interpreted in light of study quality, risk of bias, consistency of results, and biological plausibility.

2.8. Data Synthesis

Data synthesis was performed using a qualitative approach to identify key molecular findings, interactions, and knowledge gaps. Findings were grouped according to shared signaling pathways relevant to SGC-mediated pain modulation and opioid responses. Additional studies were considered to support interpretation and contextualize mechanisms where direct evidence was limited.

2.9. Reporting Bias Assessment

Publication bias could not be formally assessed using statistical methods (e.g., funnel plot asymmetry tests) due to insufficient quantitative data for meta-analysis.

2.10. Ethical Considerations

As this study is based exclusively on previously published data, no ethical approval was required.

3. Results

3.1. Overview of the Included Studies

A systematic literature search was conducted in four electronic databases: Scopus, PubMed, Web of Science, and Embase. Screening and study selection were performed using the Rayyan platform.

A total of 111 records were identified, including 22 from Scopus, 18 from PubMed, 30 from Web of Science, and 41 from Embase. After removal of 47 duplicate records, 64 studies remained for title and abstract screening. Of these, 42 records were excluded.

Twenty-two full-text articles were assessed for eligibility. Three studies were excluded after full-text review for the following reasons: lack of focus on SGCs ($n = 1$), absence of opioid- or morphine-related outcomes ($n = 1$), and inappropriate study design ($n = 1$). Ultimately, 19 studies were included in this review. A flowchart illustrating the selection process is presented in Figure 1.

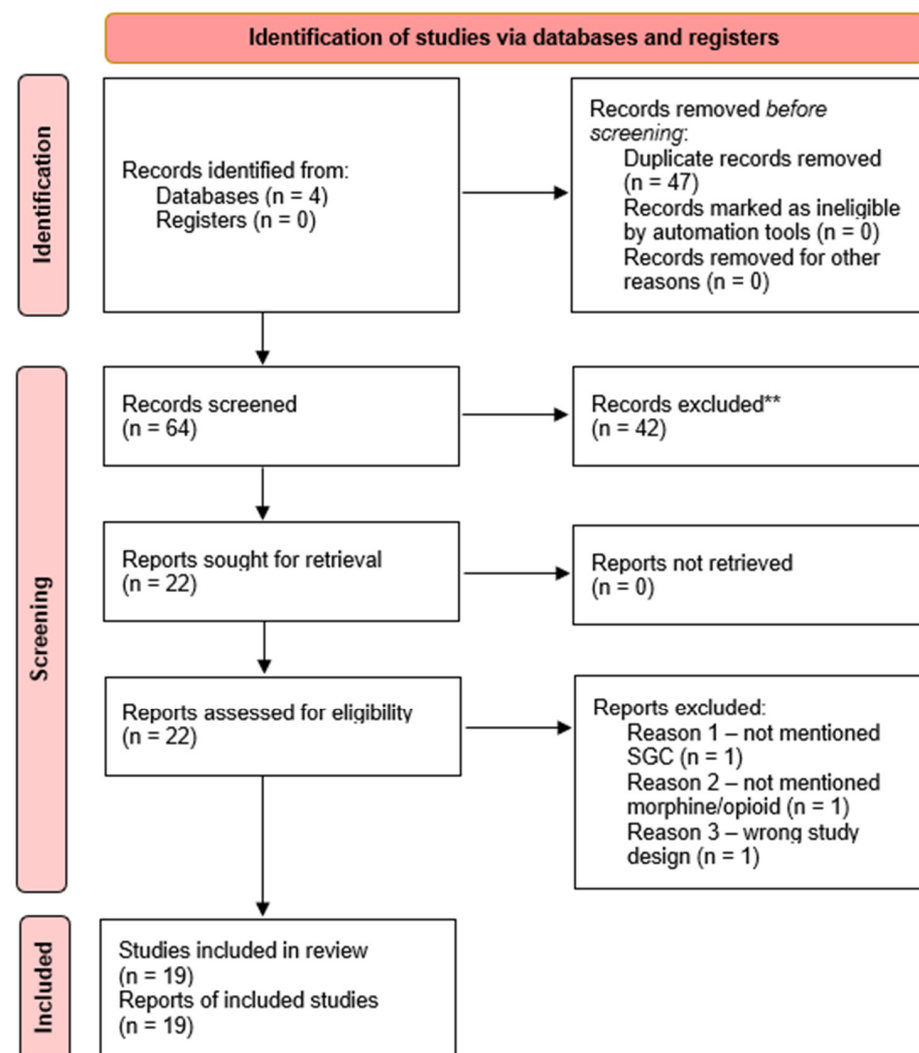


Figure 1. Flowchart of the study selection process according to PRISMA 2020 guidelines. ** Human reviewers excluded all 42 records during title and abstract screening; no automation tools were used in this process.

3.2. Period of Publication, Experimental Models, and Study Designs

The included studies covered a 20-year period (2005 to 2025). Most of the studies ($n = 14$; 73.7%) were performed in vivo, followed by studies that used in vivo and in vitro methods ($n = 3$; 15.8%); one study used in vivo and electrophysiological methods ($n = 1$; 5.3%), and there was one human translational study ($n = 1$; 5.3%). Although neuropathic pain was the most prevalent type of pain studied ($n = 10$; 52.6%), there was substantial variation and even greater variability in the animal pain models used, with chronic constriction injury (CCI) of the sciatic nerve being the most prevalent ($n = 3$; 15.8%), followed by chronic administration of morphine ($n = 2$; 10.5%) and plantar incision with remifentanyl infusion ($n = 2$; 10.5%). These findings are presented in Table 2.

Table 2. Summary of animal pain models and study designs.

Study	Year	Type of Pain	Study Design	Animal Pain Model
Peters et al., [17]	2005	Cancer pain (bone)	In vivo	Injection of osteolytic sarcoma cells into the femur
Wei et al., [18]	2007	Neuropathic pain	In vivo	Peri-sciatic administration of recombinant rat TNF- α (rrTNF)-induced mechanical allodynia mode
Chichorro et al., [19]	2009	Neuropathic pain	In vivo	CION
Mika et al., [20]	2010	Neuropathic pain	In vivo	CCI of the sciatic nerve
Wilson et al., [21]	2011	Opioid-induced hyperalgesia	In vivo and in vitro	Chronic administration of morphine
Berta et al., [22]	2012	Opioid-induced hyperalgesia	In vivo	Subcutaneous injection of morphine
Romero et al., [23]	2013	Postoperative pain and neuropathic pain induced by opioid	In vivo	Plantar incision with remifentanyl infusion
Hironaka et al., [24]	2014	Cancer pain (gingival squamous cell carcinoma)	In vivo	Implanting Walker 256 carcinosarcoma cells into the lower gingiva
Liu et al., [25]	2017	Postoperative pain and neuropathic pain induced by opioid	In vivo	Plantar incision with remifentanyl infusion
Silva et al., [26]	2017	Acute herpetic neuralgia	In vivo	HSV-1 infection-induced herpetic neuralgia model
Kwiatkowski et al., [27]	2020	Neuropathic pain	In vivo	CCI of the sciatic nerve
Zhang et al., [28]	2020	Chronic headache pain associated with PTSD	In vivo	SPS combined with SNP-induced hyperalgesia
Pawlik et al., [29]	2021	Neuropathic pain	In vivo	CCI of the sciatic nerve
Staal et al., [30]	2022	Visceral pain	In vivo	TNBS-induced visceral hypersensitivity model of colonic pain.

Table 2. Cont.

Study	Year	Type of Pain	Study Design	Animal Pain Model
Yamakita et al., [31]	2023	Opioid-induced hyperalgesia	In vivo	Chronic administration of morphine
Yousuf et al., [32]	2023	Neuropathic pain	In vivo and in vitro	SNI model and primary DRG neuron culture
Staedtler et al., [33]	2024	Human nociceptive pain pathways	Human translational study	Human DRG tissue analysis using multiplex in situ hybridization
Yuan et al., [34]	2024	Neuropathic pain	In vivo and in vitro	SNL model and primary SGC cultures
Goyal et al., [35]	2025	Neuropathic pain	In vivo and electrophysiological analysis	SNI and FRICT-ION models

CCI, chronic constriction injury; CION, chronic infraorbital nerve constriction; DRG, dorsal root ganglia; FRICT-ION, friction-induced trigeminal neuropathic pain; HSV-1, herpes simplex virus type 1; PTSD, post-traumatic stress disorder; rrTNF, recombinant rat tumor necrosis factor- α ; SNI, spared nerve injury; SNL, spinal nerve ligation; SNP, sodium nitroprusside; SPS, single prolonged stress; TNBS, 2,4,6-Trinitrobenzene sulfonic acid; TNF- α , tumor necrosis factor- α .

3.3. Molecules Analyzed in the Included Studies

A variety of molecules were used across the included studies. As presented in Table 3, at least one inflammatory cytokine (e.g., interleukin-1 beta, IL-1 β , or tumor necrosis factor- α , TNF- α) was used in six studies ($n = 6$; 31.6%); morphine in two studies ($n = 2$; 10.5%); nociceptive/orphanin FQ (N/OFQ), a neuropeptide that acts as a natural ligand of the opioid receptor-like 1 (ORL1/OPMR1/NOP receptor), in one study ($n = 1$; 5.3%); OPMR1 in one study ($n = 1$; 5.3%); and naloxone, an antagonist of the opioid receptors μ , δ , and κ , in one study ($n = 1$; 5.3%). Behavioral assays (BAs) were used in 12 studies ($n = 12$; 63.2%); immunohistochemistry (IHC) in 12 studies ($n = 12$; 63.2%); and qPCR in 7 studies ($n = 7$; 58.3%). SGCs were studied directly in 14 studies ($n = 14$; 73.68%); sensory neurons in 12 studies ($n = 12$; 63.2%); DRG in 14 studies ($n = 14$; 73.68%); and TG in 3 studies ($n = 3$; 15.79%).

Table 3. Summary of molecules analyzed in each study.

Study	Molecule/ Substance Analyzed	Brief Description of the Molecule	Technique Used for Analysis	Target Cell Type	Brief Description of the Observed Effect Caused by the Molecule
Peters et al., [17]	Gabapentin	An anticonvulsant drug that modulates calcium channels to reduce neuronal excitability	BA and IHC	Sensory neurons in DRG	Gabapentin inhibited the hyperexcitability of sensory neurons, reducing pain behavior. The study did not evaluate specific protein upregulation or downregulation in detail.

Table 3. Cont.

Study	Molecule/ Substance Analyzed	Brief Description of the Molecule	Technique Used for Analysis	Target Cell Type	Brief Description of the Observed Effect Caused by the Molecule
Wei et al., [18]	TNF- α , TNFR1, NF- κ B	TNF- α is a pro-inflammatory cytokine involved in neuroinflammatory signaling; TNFR1 is its receptor; NF- κ B is a transcription factor associated with inflammatory responses	BA, IHC, WB, and EMSA	Sensory neurons and SGCs in DRG	Peri-sciatic administration of TNF- α increased TNFR1 expression and activated NF- κ B signaling in DRG neurons and SGCs. This neuroinflammatory response was associated with bilateral mechanical allodynia and enhanced neuronal excitability.
Chichorro et al., [19]	Endothelin ETA and ETB receptor antagonists (BQ-123, BQ-788, atrasentan, A-192621, bosentan)	Endothelin receptors are G-protein-coupled receptors involved in vasoconstriction and nociceptive signaling	BA and IHC	Neurons and SGCs in TG	The antagonists inhibited the activation of endothelin ETA and ETB receptors, reducing orofacial thermal hyperalgesia induced by infraorbital nerve constriction. The study did not evaluate the upregulation or downregulation of specific proteins.
Mika et al., [20]	Minocycline	A tetracycline antibiotic that inhibits microglial activation	BA and RT-PCR (qPCR)	Microglia in the spinal cord, SGCs in DRG	Minocycline inhibited the injury-induced activation of microglia and SGCs, reducing the upregulation of prodynorphin and pronociceptin mRNA in the DRG. This resulted in decreased neuropathic pain behaviors.
Wilson et al., [21]	CXCR4 and SDF1/CXCL12	CXCR4 is a chemokine receptor; SDF1/CXCL12 is its ligand, involved in immune cell trafficking and neuronal signaling	IHC, in situ hybridiza- tion, and Ca ²⁺ imaging	SGCs and sensory neurons in DRG	Repeated morphine treatment increased SDF1 mRNA in sensory neurons and activated CXCR4 signaling in both SGCs and neurons. This dual activation contributed to opioid-induced hyperalgesia, with the CXCR4 antagonist AMD3100 reversing these effects and reducing hyperalgesia.

Table 3. Cont.

Study	Molecule/ Substance Analyzed	Brief Description of the Molecule	Technique Used for Analysis	Target Cell Type	Brief Description of the Observed Effect Caused by the Molecule
Berta et al., [22]	Morphine, MMP-9, IL-1 β	Morphine is an opioid analgesic; MMP-9 is an enzyme that modulates the extracellular matrix; IL-1 β is a pro-inflammatory cytokine	IHC, Western blot (WB), qPCR	SGCs in DRG	Morphine activated SGCs through MMP-9-dependent mechanisms, leading to the upregulation of IL-1 β within SGCs. This upregulation, in turn, increased the excitability of nearby sensory neurons, contributing to the attenuation of morphine-induced analgesia.
Romero et al., [23]	Naloxone	An opioid antagonist used to challenge and reveal latent pain sensitization	IHC	SGCs in DRG and astrocytes in the spinal cord	Surgery induced activation of SGCs and astrocytes, with persistent glial activation (indicated by GFAP) observed up to 21 days. Naloxone reactivated SGCs and astrocytes (GFAP-positive) but did not affect microglia (Iba1-positive).
Hironaka et al., [24]	TRPV1, TRPV2	TRPV1 and TRPV2 are ion channels involved in pain sensation upregulated in response to cancer pain	IHC	Neurons and SGCs in TG	Tumor inoculation led to the upregulation of TRPV1 and TRPV2 in neurons, particularly in small to large neurons. SGCs were activated, as indicated by increased GFAP expression, encircling medium and large neurons. This dual activation likely contributed to the development and maintenance of mechanical allodynia in the affected regions.

Table 3. Cont.

Study	Molecule/ Substance Analyzed	Brief Description of the Molecule	Technique Used for Analysis	Target Cell Type	Brief Description of the Observed Effect Caused by the Molecule
Liu et al., [25]	NAC, MMP-9, IL-1 β	NAC is an antioxidant that inhibits MMP-9; MMP-9 is an enzyme that facilitates neuroinflammation; IL-1 β is a pro-inflammatory cytokine	Colorimetric detection, WB, and IHC	Neurons and SGCs in DRG	Remifentanyl treatment increased MMP-9 activity in the DRG, activating SGCs. These activated SGCs released IL-1 β , contributing to an inflammatory response that increased neuronal excitability and pain. NAC inhibited MMP-9 activity, reducing IL-1 β release from SGCs, dampening inflammation, and decreasing postoperative hyperalgesia.
Silva et al., [26]	TNF- α , TNFR1, Kir4.1	TNF- α is a pro-inflammatory cytokine; TNFR1 is its receptor; Kir4.1 is a potassium channel involved in extracellular ion homeostasis	IHC, qPCR, BA, and flow cytometry	SGCs, macrophages, neutrophils, and sensory neurons in DRG	HSV-1 infection induced infiltration of macrophages and neutrophils into DRG, increasing TNF- α production and downregulating Kir4.1 expression in SGCs. This was associated with neuronal hyperexcitability and mechanical allodynia.
Kwiatkowski et al., [27]	Cenicriviroc, CCR2, CCR5, IL-1 β , IL-6, IL-18, CCL3	Cenicriviroc is a dual CCR2/CCR5 antagonist; cytokines and chemokines involved in neuroinflammation and opioid dysfunction	BA, qPCR, WB, and IHC	SGCs, microglia/macrophages, and sensory neurons	Blockade of CCR2/CCR5 reduced glial activation, inflammatory cytokine expression, and neuropathic pain behaviors while enhancing morphine and buprenorphine analgesia.
Zhang et al., [28]	Nociceptin/orphanin FQ (N/OFQ), NOP receptor, GFAP	N/OFQ is a neuropeptide involved in pain and stress responses; NOP is its receptor; GFAP is a marker of glial activation	qPCR, ELISA, IHC, and BA	SGCs in TG and DRG	Traumatic stress combined with chronic headache pain increased N/OFQ signaling and GFAP expression in sensory ganglia, suggesting enhanced SGC activation during PTSD-associated chronic pain.
Pawlik et al., [29]	CCR3, CCL7, CCL11, IL-6, SB328437	CCR3 is a chemokine receptor; CCL7 and CCL11 are inflammatory chemokines; SB328437 is a CCR3 antagonist	qPCR, WB, BA, and IHC	SGCs, immune cells, and sensory neurons in DRG	CCR3 blockade reduced neuroinflammation, glial activation, cytokine expression, and neuropathic pain while enhancing morphine and buprenorphine analgesia.

Table 3. *Cont.*

Study	Molecule/ Substance Analyzed	Brief Description of the Molecule	Technique Used for Analysis	Target Cell Type	Brief Description of the Observed Effect Caused by the Molecule
Staal et al., [30]	Lu AF27139, P2X7 receptor, pro- inflammatory prostanoids (PGE2, LTB4)	Lu AF27139 is a selective antagonist of the P2X7 receptor; P2X7 receptors are ion channels involved in inflammatory and pain signaling; prostanoids like PGE2 and LTB4 are inflammatory mediators	IHC, BA, and liquid chromatogra- phy–tandem mass spec- trometry (LC- MS/MS)	SGCs, macrophages, and spinal microglia	Lu AF27139 inhibited P2X7 receptors, reducing colonic hypersensitivity and central levels of pro-inflammatory prostanoids (PGE2 and LTB4). This was associated with decreased neuroinflammation and visceral pain.
Yamakita et al., [31]	Morphine, ERK1/2, TLR4, cytokines (IL-1 α , TNF- α)	Morphine is an opioid analgesic that can paradoxically induce hyperalgesia; ERK1/2 is involved in pain sensitization; TLR4 is a receptor in immune response; IL-1 α and TNF- α are pro-inflammatory cytokines	WB and BA	Neurons and SGCs in DRG	Morphine increased ERK1/2 phosphorylation and pro-inflammatory cytokine expression in neurons and SGCs through TLR4-dependent mechanisms. Inhibition of TLR4 signaling reduced ERK1/2 activation and attenuated morphine-induced hyperalgesia.
Yousuf et al., [32]	σ 2R/TMEM97 ligand FEM-1689, p-eIF2 α , ISR markers	FEM-1689 is a selective σ 2R/TMEM97 ligand; ISR markers are associated with cellular stress responses	BA, IF, WB, primary DRG cultures, and human sensory neuron assays	DRG neurons and human sensory neurons	FEM-1689 reduced neuropathic pain behaviors and inhibited the integrated stress response, decreasing p-eIF2 α signaling and promoting neuronal recovery independently of opioid pathways.
Staedtler et al., [33]	OPRM1, OPRK1, MRGPRD, TRPV1	Opioid receptors and nociceptive markers involved in sensory neuron classification and pain modulation	Multiplex in situ hy- bridization	Human sensory neurons and SGCs in DRG	Distinct human nociceptive populations based on OPRM1 expression were identified, with predominant OPRK1 expression observed in SGCs within human DRG tissue.
Yuan et al., [34]	TFAP2A, Grin1/NR1, IL-1 β , IL-6, TNF- α	TFAP2A is a transcription factor; Grin1 encodes the NR1 NMDA receptor subunit	qPCR, WB, dual- luciferase assay, electrophys- iology, and primary SGC cultures	SGCs, Schwann cells, and sensory neurons in DRG	TFAP2A upregulation increased Grin1 expression and promoted inflammatory signaling in SGCs, contributing to neuronal hyperexcitability and neuropathic pain maintenance.

Table 3. Cont.

Study	Molecule/ Substance Analyzed	Brief Description of the Molecule	Technique Used for Analysis	Target Cell Type	Brief Description of the Observed Effect Caused by the Molecule
Goyal et al., [35]	Humanized P2X4 scFv antibody, P2X4 receptor	P2X4 is an ATP-gated purinergic receptor involved in neuroinflammation and pain signaling	BA, patch- clamp electrophys- iology, and FosTRAP neuronal recordings	Sensory neurons and glial cells in DRG, TG, spinal cord, and vIPAG	Blockade of P2X4 signaling reduced neuronal excitability and attenuated neuropathic pain behaviors in peripheral and central pain pathways.
CCL11, C-C motif chemokine ligand 11; CCL3, C-C motif chemokine ligand 3; CCL7, C-C motif chemokine ligand 7; CCR2, C-C chemokine receptor type 2; CCR3, C-C chemokine receptor type 3; CCR5, C-C chemokine receptor type 5; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; DRG, dorsal root ganglia; ELISA, enzyme-linked immunosorbent assay; EMSA, electrophoretic mobility shift assay; ERK1/2, extracellular signal-regulated kinase 1/2; ETA, endothelin receptor type A; ETB, endothelin receptor type B; FosTRAP, Fos-targeted recombination in active populations; GFAP, glial fibrillary acidic protein; Grin1, glutamate ionotropic receptor NMDA type subunit 1; HSV-1, herpes simplex virus type 1; IF, immunofluorescence; IHC, immunohistochemistry; IL-1 α , interleukin-1 alpha; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; IL-18, interleukin-18; ISR, integrated stress response; Kir4.1, inward-rectifier potassium channel 4.1; LC-MS/MS, liquid chromatography–tandem mass spectrometry; LTb4, Leukotriene B4; MMP-9, matrix metalloproteinase-9; mRNA, messenger ribonucleic acid; MRGPRD, Mas-related G-protein-coupled receptor member D; N/OFQ, nociceptin/orphanin FQ; NAC, N-acetyl-cysteine; NF- κ B, nuclear factor kappa B; NOP, nociceptin opioid peptide receptor; NR1, N-methyl-D-aspartate receptor subunit 1; OPRK1, kappa opioid receptor; OPRM1, mu opioid receptor; P2X4, P2X purinoceptor 4; P2X7, P2X purinoceptor 7; p-eIF2 α , phosphorylated eukaryotic initiation factor 2 alpha; PGE2, prostaglandin E2; PTSD, post-traumatic stress disorder; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; scFv, single-chain variable fragment; SDF1, stromal cell-derived factor 1; SGCs, satellite glial cells; TFAP2A, transcription factor AP-2 alpha; TLR4, Toll-like receptor 4; TMEM97, transmembrane protein 97; TNF- α , tumor necrosis factor alpha; TNFR1, tumor necrosis factor receptor 1; TRPV1, transient receptor potential vanilloid 1; TRPV2, transient receptor potential vanilloid 2; vIPAG, ventrolateral periaqueductal gray; WB, Western blot; σ 2R, sigma-2 receptor.					

3.4. Activation of SGCs and Their Modulation in Pain Pathways

The role of SGC activation in modulating pain pathways and related outcomes, the impact of interventions on SGCs, and the indicators used to provide evidence of SGC activation in each study are presented in Table 4.

Table 4. Summary of SGC activation and its modulation in pain pathways.

Study	SGC Activation Indicators	Role of SGC Activation and Related Outcomes	Impact on SGC Activation
Peters et al., [17]	Increased GFAP expression on SGCs	SGCs enhanced neuronal excitability, contributing to cancer-related neuropathic pain	Not applicable (no specific intervention into SGCs)
Wei et al., [18]	Increased TNFR1 expression and NF- κ B activation in DRG neurons and SGCs	TNF- α -mediated activation of SGCs contributed to neuroinflammatory signaling, neuronal hyperexcitability, and bilateral mechanical allodynia	Inhibition of TNF- α /TNFR1 signaling attenuated NF- κ B activation and reduced pain hypersensitivity
Chichorro et al., [19]	Activation of endothelin ETA/ETB receptors on SGCs, increased GFAP	SGC activation through endothelin receptors amplified pain signaling, leading to increased orofacial pain	Endothelin receptor antagonists reduced SGC activation and associated pain

Table 4. *Cont.*

Study	SGC Activation Indicators	Role of SGC Activation and Related Outcomes	Impact on SGC Activation
Mika et al., [20]	Reduced prodynorphin and pronociceptin expression in SGCs	Minocycline inhibited SGC-driven neuropeptide production, decreasing neuron–glia signaling and reducing pain behaviors	Minocycline effectively reduced SGC activation and its pain-associated effects
Wilson et al., [21]	Increased CXCR4 expression and cytokine release (SDF1) in SGCs	SGC activation through CXCR4 exacerbated neuroinflammatory signaling, contributing to morphine-induced hyperalgesia	CXCR4 antagonist (AMD3100) reduced SGC activation and hyperalgesia
Berta et al., [22]	Upregulation of IL-1 β and MMP-9 in SGCs	SGC-mediated IL-1 β release increased neuronal activity, reducing morphine analgesia	Inhibition of MMP-9 reduced SGC activation and preserved morphine’s analgesic effect
Romero et al., [23]	Sustained increase in GFAP expression in SGCs	Persistent SGC activation maintained heightened pain sensitivity, contributing to chronic postoperative pain	Naloxone reactivated GFAP-positive SGCs during latent sensitization
Hironaka et al., [24]	Increased GFAP-positive SGCs surrounding medium and large TG neurons	SGC activation via TRPV channels potentiated pain signals from cancer-affected neurons, exacerbating cancer-related pain	TRPV channel blockers reduced SGC activation and associated pain
Liu et al., [25]	Increased MMP-9 activity and IL-1 β release associated with activated SGCs	NAC reduced SGC-driven inflammation, decreasing neuronal sensitivity and hyperalgesia	NAC treatment effectively inhibited SGC activation, attenuating hyperalgesia
Silva et al., [26]	Downregulation of Kir4.1 channels and increased TNF- α signaling in SGCs	Altered potassium buffering by activated SGCs promoted neuronal hyperexcitability and the development of acute herpetic neuralgia	Reduction of TNF- α -mediated neuroinflammation attenuated SGC dysfunction and pain hypersensitivity
Kwiatkowski et al., [27]	Increased GFAP-positive cells and chemokine receptor signaling (CCR2/CCR5) in DRG	SGC activation contributed to neuroinflammation, cytokine release, and reduced opioid responsiveness during neuropathic pain	Cenicriviroc reduced SGC activation and inflammatory signaling and enhanced opioid analgesia
Zhang et al., [28]	Increased GFAP expression and enhanced N/OFQ-NOP signaling in sensory ganglia	Activated SGCs contributed to enhanced nociceptive sensitization associated with PTSD-related chronic headache pain	No direct SGC-targeted intervention was performed, but increased glial activation correlated with pain exacerbation
Pawlik et al., [29]	Increased GFAP-positive cells and elevated CCR3-associated inflammatory signaling	SGC activation amplified neuropathic pain and neuroimmune signaling pathways	CCR3 antagonism reduced SGC activation and inflammatory mediators and potentiated opioid analgesia
Staal et al., [30]	Reduced P2X7-mediated activation of SGCs, decreased GFAP	Inhibition of P2X7 receptors in SGCs reduced neuroinflammatory responses, alleviating visceral pain	P2X7 receptor antagonists decreased SGC activation and visceral pain

Table 4. Cont.

Study	SGC Activation Indicators	Role of SGC Activation and Related Outcomes	Impact on SGC Activation
Yamakita et al., [31]	Phosphorylation of ERK1/2 and activation of TLR4 in SGCs	SGCs mediated TLR4 signaling, intensifying ERK1/2 pathways, leading to severe morphine-induced hyperalgesia	TLR4 antagonists reduced ERK1/2 activation in SGCs, mitigating hyperalgesia
Yousuf et al., [32]	σ 2R/TMEM97 expression identified in SGCs and sensory neurons	SGC-associated stress response pathways contributed to neuropathic pain maintenance through integrated stress response signaling	FEM-1689 reduced ISR activation and attenuated neuropathic pain behaviors
Staedtler et al., [33]	Predominant expression of OPRK1 in SGCs of human DRG	Findings suggested that SGCs may directly participate in opioid-mediated modulation of human nociceptive pathways	No interventional modulation was performed
Yuan et al., [34]	Increased TFAP2A and Grin1 expression in SGCs after spinal nerve ligation	Activated SGCs contributed to glutamatergic signaling, inflammatory cytokine release, and neuronal hyperexcitability	Tfap2a silencing reduced SGC-mediated inflammation and neuropathic pain behaviors
Goyal et al., [35]	Increased P2X4-related signaling in sensory ganglia	Glial-associated purinergic signaling contributed to enhanced neuronal excitability and chronic neuropathic pain	Humanized P2X4 scFv antibody reduced neuronal excitability and attenuated neuropathic pain behaviors

AMD3100, CXCR4 antagonist; CCR2, C-C chemokine receptor type 2; CCR3, C-C chemokine receptor type 3; CCR5, C-C chemokine receptor type 5; CXCR4, C-X-C chemokine receptor type 4; DRG, dorsal root ganglia; ERK1/2, extracellular signal-regulated kinase 1/2; ETA, endothelin receptor type A; ETB, endothelin receptor type B; GFAP, glial fibrillary acidic protein; Grin1, glutamate ionotropic receptor NMDA type subunit 1; IL-1 β , interleukin-1 beta; Kir4.1, inward-rectifier potassium channel 4.1; MMP-9, matrix metalloproteinase-9; N/OFQ, nociceptin/orphanin FQ; NAC, N-acetyl-cysteine; NF- κ B, nuclear factor kappa B; NOP, nociceptin opioid peptide receptor; OPRK1, kappa opioid receptor; P2X4, P2X purinoceptor 4; P2X7, P2X purinoceptor 7; PTSD, post-traumatic stress disorder; scFv, single-chain variable fragment; SDF1, stromal cell-derived factor 1; SGCs, satellite glial cells; TFAP2A, transcription factor AP-2 alpha; TG, trigeminal ganglia; TLR4, Toll-like receptor 4; TMEM97, transmembrane protein 97; TNF- α , tumor necrosis factor alpha; TNFR1, tumor necrosis factor receptor 1; σ 2R, sigma-2 receptor.

3.5. SGC-Mediated Modulation of Opioid Signaling and Pain Sensitization

Table 5 shows the molecules or receptors located in SGCs that directly affected the opioid pathway in each included study, changes in opioid pathway signaling, and implications for opioid efficacy and sensitization. While IL-1 β was used to evaluate opioid neurotransmission activity in four studies ($n = 4$; 21%), most ($n = 9$; 47.4%) did not evaluate a specific SGC molecule or receptor or changes in opioid neurotransmission.

Table 5. Summary of potential involvement of SGCs in opioid-related signaling mechanisms.

Study	SGC Receptor/Molecule Influencing Opioid Pathway	Opioid Pathway Involved	Implications for Opioid Efficacy and Sensitization
Peters et al., [17]	Not evaluated	Not evaluated	Not evaluated
Wei et al., [18]	Not evaluated	Not evaluated	Not evaluated
Chichorro et al., [19]	Not evaluated	Not evaluated	Not evaluated
Mika et al., [20]	Not evaluated	Not evaluated	Not evaluated

Table 5. Cont.

Study	SGC Receptor/Molecule Influencing Opioid Pathway	Opioid Pathway Involved	Implications for Opioid Efficacy and Sensitization
Wilson et al., [21]	CXCR4 receptor, SDF1 (cytokine)	Repeated morphine treatment increased SDF1/CXCL12 signaling and CXCR4 activation in SGCs and sensory neurons	May contribute to opioid tolerance by increasing pain sensitivity and reducing overall efficacy of opioid analgesia
Berta et al., [22]	IL-1 β (cytokine)	Morphine binds to MOR on neurons, leading to MMP-9 release, which activates SGCs; activated SGCs release IL-1 β , which binds to IL-1R on neurons, reducing analgesic effects and increasing pain sensitivity	Accelerates opioid tolerance by promoting chronic inflammation and altering neuronal receptor sensitivity
Romero et al., [23]	GFAP	Naloxone administration reactivated GFAP-positive SGCs after surgery and remifentanyl exposure, suggesting involvement of opioid and non-opioid signaling mechanisms in latent pain sensitization	Suggested persistent glial activation associated with opioid-sensitive latent pain sensitization
Hironaka et al., [24]	IL-1 β (cytokine)	Remifentanyl increases oxidative stress in neurons, causing MMP-9 release; MMP-9 activates SGCs to release IL-1 β , which binds to IL-1R on neurons, reducing opioid analgesia; NAC reduces this stress, preventing these effects	Reduces opioid tolerance by preventing oxidative damage and maintaining receptor sensitivity
Liu et al., [25]	MMP-9, IL-1 β , MOR	Remifentanyl infusion increased MMP-9 activation in MOR-expressing DRG neurons, promoting IL-1 β cleavage and SGC activation in DRG	Enhanced neuron–glia inflammatory signaling may contribute to opioid-induced hyperalgesia and reduced opioid analgesic efficacy
Silva et al., [26]	Not evaluated	Not evaluated	Not evaluated
Kwiatkowski et al., [27]	CCR2, CCR5, IL-1 β , IL-6, IL-18, CCL3	CCR2/CCR5 signaling contributed to neuroinflammatory activation in DRG and spinal cord, reducing opioid analgesic efficacy; blockade of CCR2/CCR5 enhanced morphine and buprenorphine analgesia	May contribute to impaired opioid responsiveness during neuropathic pain
Zhang et al., [28]	NOP receptor, N/OFQ	Increased N/OFQ signaling was associated with enhanced pain sensitization in DRG and TG during chronic stress and headache pain conditions	Possible involvement in dysregulation of opioid-related pain pathways under chronic stress conditions

Table 5. Cont.

Study	SGC Receptor/Molecule Influencing Opioid Pathway	Opioid Pathway Involved	Implications for Opioid Efficacy and Sensitization
Pawlik et al., [29]	CCR3, CCL7, CCL11	CCR3-mediated inflammatory signaling contributed to neuropathic pain and reduced opioid analgesic potency; CCR3 blockade enhanced morphine and buprenorphine analgesia	May contribute to opioid tolerance and impaired opioid responsiveness during neuropathic pain
Staal et al., [30]	Not evaluated	Not evaluated	Not evaluated
Yamakita et al., [31]	TLR4, ERK1/2, IL-1 α , TNF- α	Morphine-induced hyperalgesia was associated with TLR4-dependent ERK1/2 activation and pro-inflammatory cytokine expression in neurons and SGCs	Suggested contribution of SGC-mediated neuroinflammation to opioid-induced hyperalgesia
Yousuf et al., [32]	Not evaluated	Not evaluated	Not evaluated
Staedtler et al., [33]	OPRK1	OPRK1 expression was predominantly identified in satellite glial cells in human DRG tissue	Possible role of SGCs in opioid-related signaling in human sensory ganglia
Yuan et al., [34]	Not evaluated	Not evaluated	Not evaluated
Goyal et al., [35]	Not evaluated	Not evaluated	Not evaluated

CCL3, C-C motif chemokine ligand 3; CCL7, C-C motif chemokine ligand 7; CCL11, C-C motif chemokine ligand 11; CCR2, C-C chemokine receptor type 2; CCR3, C-C chemokine receptor type 3; CCR5, C-C chemokine receptor type 5; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; DRG, dorsal root ganglia; ERK1/2, extracellular signal-regulated kinase 1/2; GFAP, glial fibrillary acidic protein; IL-1 α , interleukin-1 alpha; IL-1 β , interleukin-1 beta; IL-1R, interleukin-1 receptor; IL-6, interleukin-6; IL-18, interleukin-18; MMP-9, matrix metalloproteinase-9; MOR, mu opioid receptor; N/OFQ, nociceptin/orphanin FQ; NAC, N-acetyl-cysteine; NOP, nociceptin opioid peptide receptor; OPRK1, kappa opioid receptor; SDF1, stromal cell-derived factor 1; SGCs, satellite glial cells; TG, trigeminal ganglia; TLR4, Toll-like receptor 4; TNF- α , tumor necrosis factor alpha.

3.6. Risk of Bias Assessment

The included studies' methodological quality was assessed using the OHAT Risk of Bias Tool. Overall, most studies presented a low to moderate risk of bias across exposure and outcome assessment. However, limitations related to reporting bias, attrition bias, and insufficient methodological reporting were observed in several studies. Detailed assessments are presented in Table 6, and the complete risk of bias evaluation is available in the Supplementary Materials.

Table 6. Summary of risk of bias assessment of included studies according to the OHAT Tool (low = definitely/probably low risk of bias; moderate = mixed classification across detection domains; high = probably high risk of bias).

Study	Selection Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Peters et al., [17]	Low	Low	High	High	Low
Wei et al., [18]	High	Low	High	High	High
Chichorro et al., [19]	Low	Low	High	High	High
Mika et al., [20]	Low	Moderate	High	High	High

Table 6. *Cont.*

Study	Selection Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Wilson et al., [21]	Low	Low	High	High	High
Berta et al., [22]	High	Low	Low	High	High
Romero et al., [23]	High	Low	Low	High	High
Hironaka et al., [24]	High	Low	Low	High	High
Liu et al., [25]	Low	Low	Low	Low	Low
Silva et al., [26]	High	Low	Low	High	High
Kwiatkowski et al., [27]	Low	Low	Low	Low	Low
Zhang et al., [28]	Low	Low	Low	Low	Low
Pawlik et al., [29]	Low	Low	Low	Low	Low
Staal et al., [30]	Low	Moderate	Low	High	High
Yamakita et al., [31]	Low	Moderate	Low	High	High
Yousuf et al., [32]	Low	Low	Low	Low	Low
Staedtler et al., [33]	High	Low	Low	Low	Low
Yuan et al., [34]	Low	Low	Low	Low	Low
Goyal et al., [35]	Low	Low	Low	Low	Low

4. Discussion

4.1. SGC Biology: From Homeostatic Functions to Pain Pathophysiology

SGCs are part of the PNS, which surrounds the cell bodies of sensory neurons in various ganglia, including the DRG, TG, cochlear ganglia, and vagal ganglia. These structures transmit sensory information from the periphery, face, and internal organs to the CNS [36–38].

SGCs demonstrate remarkable plasticity, evidenced by their ability to express typical stem cell markers, alter their morphology under in vitro conditions, and differentiate into various cell types, including neurons [39–41].

One of the most striking manifestations of this plasticity is the expression of undifferentiated cell markers, such as the transcription factors Sox2 and Sox10 [42–45]. Sox2, widely recognized as a stem cell marker, demonstrates the potential of SGCs to act as progenitor cells and differentiate into other cell types, such as oligodendrocytes and Schwann cells [46].

In addition to expressing stem cell markers, SGCs also exhibit a notable ability to alter their morphology when cultured under in vitro conditions. Studies show that after being isolated from their associated neurons, these cells initiate migration, losing their original shape and adopting a spindle-shaped morphology. This transformation suggests that outside of the restrictive environment of the ganglion, SGCs possess significant phenotypic plasticity [47–49]. This may be due to components of the extracellular matrix, such as laminin or other compounds derived from SGC–neuron interactions, although this remains under-investigated [50].

Furthermore, SGCs possess stem-cell-like characteristics and can differentiate into multiple cell types, including neurons. Research on DRG cultures reveals that these cells can differentiate into Schwann cells and functional sensory neurons, demonstrating their multipotency [40]. This multipotent differentiation capacity, as in Schwann cell precursors, highlights the importance of SGCs in nerve regeneration and tissue repair.

SGCs form the neuron–glial unit. Due to their flattened morphology, they envelop neuronal cell bodies, maintaining a narrow extracellular cleft of approximately 20 nm

between their plasma membranes. The neuron–SGC unit is surrounded by basal lamina and a connective tissue capsule [51], allowing SGCs to quickly monitor and adjust the extracellular environment in response to changes in neuronal activity [51–53]. Within each SGC–neuron unit, glial cells are often interconnected via gap junctions primarily composed of connexins such as Cx43 and Cx32. Under physiological conditions, communicating junctions between SGCs of different SGC–neuron units are less common [54–57].

Although SGCs do not conduct action potentials, they express a variety of other ion channels essential for their role in regulating the neuronal environment. Among these are potassium channels. Neurons release potassium (K^+) into the extracellular space during action potential propagation. An increase in extracellular K^+ levels is believed to lower the neuronal firing threshold, leading to hyperexcitability. SGCs help sustain extracellular K^+ levels by taking up excess K^+ . The most well-known channel for this function in SGCs is Kir4.1 (inwardly rectifying potassium channel 4.1). Recently, small conductance calcium-activated potassium channels (SK channels) have also been observed to play a role in this context [58–62].

In addition to ion homeostasis, SGCs contribute to neurotransmitter regulation, particularly glutamate metabolism. Through the expression of glutamine synthetase, SGCs convert glutamate into glutamine, preventing its excessive accumulation in the extracellular space and reducing the risk of excitotoxicity and neuronal damage [63–67].

The most studied type of communication between neurons and SGCs is purinergic signaling. Sensory neurons can release ATP, which in turn activates purinergic receptors on SGCs. Under homeostatic conditions, P2Y receptors, which are G-protein-coupled and include subtypes such as P2Y1, P2Y2, P2Y4, P2Y6, P2Y12, and P2Y13, regulate intracellular calcium levels in response to ATP released by sensory neurons [68–73]. P2X receptors, which are ion channels and include subtypes such as P2X2, P2X4, P2X5, and P2X7, enable the rapid influx of calcium and sodium ions in response to ATP. Together, these receptors help regulate neuronal excitability and the maintenance of ionic balance [70,71,74–76].

Gamma-aminobutyric acid (GABA) has also been shown to modulate SGC function. Released from neuronal cell bodies in response to increased extracellular K^+ , GABA can bind to GABA_B receptors on SGCs, enhancing their K^+ buffering capacity. This contributes to stabilization of the extracellular environment and helps prevent excessive neuronal firing [53,77–80]. As illustrated in Figure 2, SGCs regulate neuronal excitability through interconnected mechanisms involving gap junctions, ion buffering, neurotransmitter homeostasis, purinergic signaling, and inflammatory mediators.

Current evidence no longer supports the view of SGCs as passive structural elements. Instead, they are now recognized as active contributors to chronic pain initiation and maintenance. One of the first changes following injury is an impact on SGC intercommunication. Gap-junction-mediated coupling is significantly enhanced following peripheral nerve damage, with upregulation of connexins such as Cx43 and Cx26. Increased communication is no longer restricted to individual neuron–glial units but extends to adjacent units, promoting a broader network of interconnected cells. As a result, SGCs exhibit increased functional coupling, which may facilitate the spread of excitatory and inflammatory signals across neighboring neurons [81–85].

Alterations in K^+ homeostasis also play a critical role in this context. Under conditions of injury or inflammation, SGCs exhibit reduced Kir4.1 channel expression, compromising their ability to buffer extracellular K^+ . The resulting accumulation of K^+ lowers the neuronal firing threshold, contributing to hyperexcitability and peripheral sensitization [52,62,86].

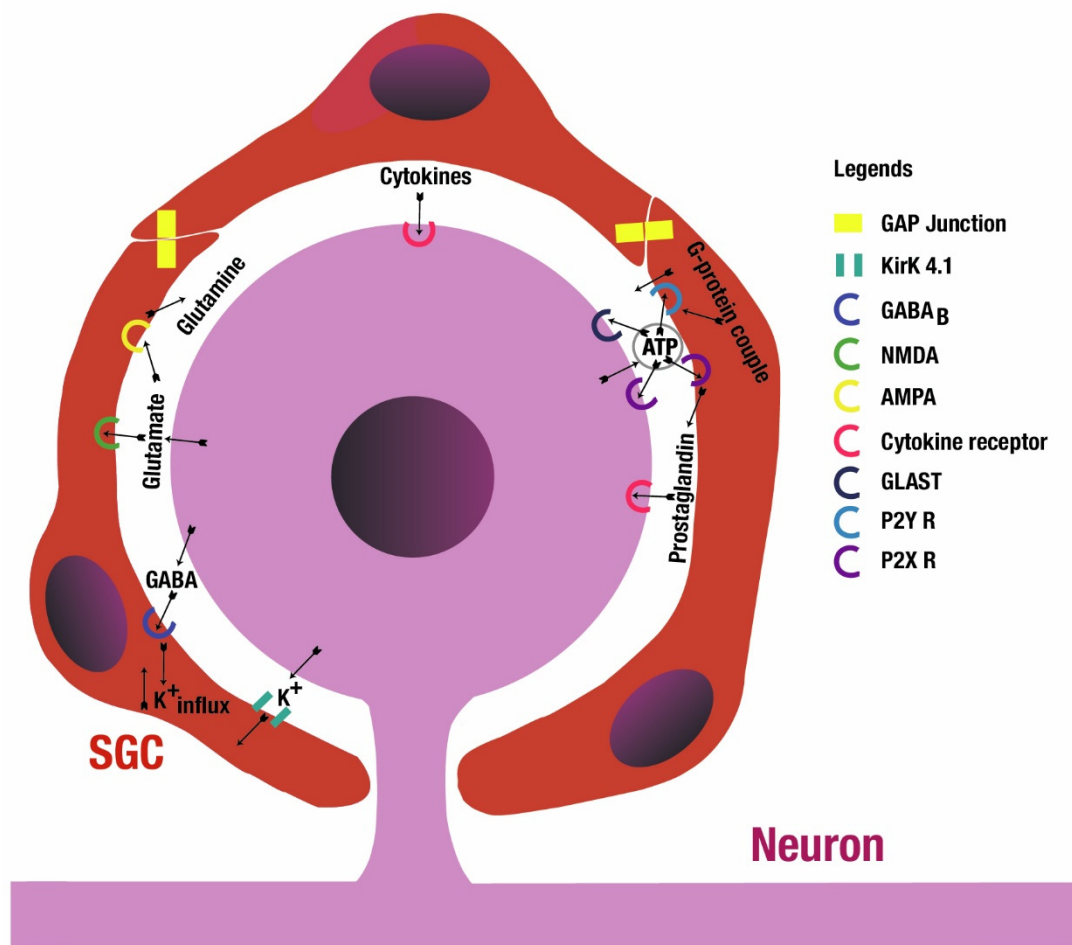


Figure 2. Representative scheme of the interaction between satellite glial cells (SGCs) and sensory neurons within sensory ganglia. SGCs envelop neuronal cell bodies and regulate neuronal excitability through multiple signaling pathways. Gap junctions mediate communication between adjacent SGCs, while Kir4.1 channels contribute to extracellular potassium buffering. Glutamate signaling occurs through NMDA and AMPA receptors, and GABA-mediated signaling occurs through GABA_B receptors. ATP released into the extracellular environment activates purinergic P2X and P2Y receptors, contributing to neuron–glia communication and inflammatory signaling. Cytokines and prostaglandins released within the ganglionic microenvironment may further modulate peripheral sensitization. GLAST transporters participate in glutamate uptake and neurotransmitter homeostasis maintenance. Adapted based on current understanding of SGC–neuron communication in pain modulation.

Purinergic signaling also appears to be altered in chronic pain models, including changes in P2X7 channels. Under homeostatic conditions, when P2X7 is activated by ATP, it functions as a cation channel, enabling the influx of ions such as calcium (Ca²⁺) and sodium (Na⁺) into the cell and the efflux of K⁺. At low ATP concentrations, P2X7 acts solely as a cation channel. However, at high ATP concentrations, such as those released in response to nerve injury, the P2X7 receptor can not only open its ion channel but also interact with pannexin-1, leading to the formation of hemichannels in the cell membrane. These hemichannels, formed by pannexin-1, are large enough to allow the passage of larger molecules out of the cell, such as ATP, NAD⁺, and other signaling molecules. This dilation and the subsequent influx of large amounts of calcium into the cell trigger a cascade of cellular responses, activating signaling pathways within SGCs that can lead to the release of pro-inflammatory cytokines, which in turn may further increase the excitability of sensory neurons and perpetuate the chronic pain cycle [61,74,87–97].

A key concept borrowed from immunology is glial activation. SGC activation is a complex process that resembles immune system cell activation in response to danger signals. One of the primary indicators of SGC activation is elevated expression of glial fibrillary acidic protein (GFAP), a classic marker of glial reactivity [98–103]. Activated SGCs also exhibit increased sensitivity to ATP [104,105]. Another proposed mechanism of glial activation involves endothelin-1 [106]. When activated, SGCs begin to produce and release pro-inflammatory cytokines, such as $\text{TNF}\alpha$, $\text{IL-1}\beta$, and IL-6 [102,107–110].

These cytokines are known to enhance neuronal excitability, contributing to peripheral sensitization and amplifying pain signals. SGCs may also play an immune role similar to that of antigen-presenting cells, as they express molecules such as MHC class II, CD40, and CD54, indicating their capacity to participate in broader immune responses [111,112].

The role of glial cells in opioid neurotransmission and the effects of analgesic opioids have also been investigated. Morphine exerts its analgesic effects primarily through activation of the mu-opioid receptor (MOR) in both the CNS and the PNS. In the CNS, MOR activation couples to inhibitory G proteins, inhibiting adenylate cyclase and reducing intracellular cyclic AMP (cAMP) levels. The reduction in cAMP levels leads to closure of voltage-dependent calcium channels at nerve terminals, decreasing the influx of calcium ions into the cells. With less calcium available, the release of excitatory neurotransmitters such as glutamate and substance P is significantly reduced. Simultaneously, morphine induces the opening of K^+ channels, leading to hyperpolarization of the cell membrane, making the cell less excitable and less likely to generate action potentials [113–115].

In the PNS, morphine also binds to MOR on neurons. Activation of these receptors in the peripheral environment triggers a signaling cascade involving the production of nitric oxide (NO), activation of guanylate cyclase, an increase in cGMP levels, and activation of protein kinase G (PKG). This cascade results in the opening of ATP-sensitive K^+ channels [116–118].

In addition to MOR, morphine also interacts with kappa (κ) and delta (δ) opioid receptors, which are involved in additional mechanisms of analgesia and other physiological responses. At kappa (κ) receptors, activation also leads to voltage-dependent Ca^{2+} channel inhibition, like mu receptors, which reduces the release of excitatory neurotransmitters and modulates pain transmission primarily in regions of the CNS associated with pain control and stress response. Furthermore, activation of kappa receptors has been associated with the induction of dysphoria and psychotomimetic effects, limiting their potential as a standalone therapeutic target for analgesia. Opioid δ receptors, on the other hand, are involved in pain modulation and neuronal plasticity. Activation of these receptors by morphine and other agonists can promote analgesia through mechanisms involving both inhibition of adenylate cyclase and activation of signaling pathways, such as mitogen-activated protein kinase (MAPK) pathways. These signaling pathways can modulate gene expression and neuronal sensitivity, influencing analgesic efficacy and adaptation to painful stimuli over time [119–122].

Beyond its direct action on neurons, morphine is metabolized in the liver into two major metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). These processes are catalyzed by the enzyme UDP-glucuronosyltransferase 2B7 (UGT2B7). While M3G is inactive in terms of analgesia and may even be associated with adverse effects such as neurotoxicity, M6G has a higher affinity for mu receptors than morphine and therefore contributes prolonged analgesic effects.

The presence of transporters at the blood–brain barrier, such as those encoded by the ABCB1 gene, can influence the efficiency with which morphine and its active metabolites, such as M6G, enter and exit the brain [123]. Genetic variations in these transporters and the enzymes that metabolize morphine can result in significant variability in responses

to morphine; for instance, individuals with certain variants of the CYP2D6 gene may metabolize codeine (a precursor to morphine) into morphine efficiently, directly impacting analgesic efficacy [124].

Morphine acts both centrally and peripherally, blocking the conduction of painful stimuli and providing pain relief. When morphine repeatedly binds to mu receptors, there is continuous activation of G-protein-coupled MORs, which initially promotes analgesia. However, prolonged activation leads to phosphorylation of the receptors by specific kinases, such as G-protein-coupled receptor kinases (GRKs). Phosphorylation of MORs facilitates the binding of a protein called β -arrestin to the receptor, which blocks G-protein-mediated signaling and promotes receptor internalization, removing it from the cell surface [125,126].

This process of MOR internalization, followed by degradation or recycling back to the cell membrane, reduces the number of receptors available for morphine to act on, decreasing opioid efficacy and clinically manifesting as tolerance. With prolonged morphine use, there is a shift in MOR coupling from predominantly Gi/Go protein signaling, which inhibits adenylate cyclase, to Gs protein signaling, which can increase adenylate cyclase activity and consequently elevate cAMP levels, promoting effects opposite to the initial analgesia [127,128].

Another important factor in morphine tolerance is the activation of glial cells in the CNS, such as microglia and astrocytes [129]. Morphine activates Toll-like receptor 4 (TLR4) on these cells, triggering an inflammatory response [130,131]. Activation of NLRP3 inflammatory cytokines, such as IL-1 β and TNF- α , increases neuroinflammation and reduces morphine's analgesic efficacy [132]. These cytokines can modify MOR expression and sensitivity, further promoting tolerance.

4.2. Evidence from the Included Studies

Unless otherwise indicated, the findings described in this section are derived directly from the 19 studies included in this systematic review; additional references cited for contextual or mechanistic interpretation represent the supporting background literature and were not part of the formal inclusion set. According to the included studies, SGC activation was consistently observed in response to different pain conditions. This activation leads to the release of pro-inflammatory cytokines, including, most notably, IL-1 β . IL-1 β acts on IL-1 receptors on neurons, promoting hyperexcitability that perpetuates chronic pain. Cytokine release forms part of a broader neuroinflammatory response that sustains pain, even in the presence of opioid analgesics [20–22,25].

The role of SGCs in sustaining neuroinflammation is particularly evident in opioid-induced hyperalgesia, as opioids like morphine and remifentanyl can paradoxically increase pain sensitivity by activating SGCs. Morphine, for example, was shown to induce MMP-9 release from neurons; MMP-9, in turn, activates SGCs to release IL-1 β . This cytokine then binds to IL-1 receptors on neurons, exacerbating pain rather than alleviating it [22,25]. This finding underscores the dual role of SGCs in both chronic pain maintenance and opioid efficacy modulation.

While generalized SGC activation has been consistently associated with chronic pain, increasing evidence suggests that specific receptor-mediated pathways may regulate neuron–glia communication within sensory ganglia. In recent years, particular attention has been directed toward chemokine, purinergic, and inflammatory signaling pathways involved in opioid-induced sensitization and maladaptive nociceptive processing.

Emerging evidence suggests that SGCs actively participate in receptor-mediated neuroimmune signaling within sensory ganglia. Rather than functioning solely as structural support cells, SGCs respond to neuronal injury, opioid exposure, and inflammatory mediators, contributing to peripheral sensitization and altered nociceptive processing. According

to the studies included in this review, chemokine-, cytokine-, and purinergic-related pathways repeatedly emerge as mechanisms associated with SGC activation and opioid-related pain modulation.

Among chemokine-related mechanisms, the CXCR4/SDF1 axis appears to play an important role in neuron–glia communication during opioid-induced hyperalgesia. Wilson et al. [21] demonstrated increased SDF1/CXCL12 signaling following repeated morphine administration, accompanied by CXCR4 activation in both sensory neurons and SGCs. These findings support the hypothesis that chronic opioid exposure promotes neuroimmune amplification within the DRG microenvironment, contributing to enhanced nociceptive sensitization and reduced opioid analgesic efficacy.

Additional evidence suggests that chemokine signaling may broadly influence opioid responsiveness during neuropathic pain conditions. Experimental blockade of CCR2/CCR5 [27] and CCR3 pathways [29] reduced inflammatory cytokine expression and glial activation while enhancing morphine and buprenorphine analgesia. Although these studies did not exclusively investigate SGC-specific mechanisms, modulation of neuroimmune signaling in sensory ganglia further supports the contribution of chemokine-mediated neuron–glia interactions to impaired opioid efficacy in chronic pain.

Inflammatory signaling pathways associated with TLR4 activation have also been implicated in opioid-related neuroplasticity. Yamakita et al. [31] observed increased ERK1/2 phosphorylation and elevated expression of pro-inflammatory cytokines, including IL-1 α and TNF- α , in neurons and SGCs following chronic morphine exposure. Although the precise contribution of SGC-specific TLR4 activation remains incompletely understood, these findings reinforce the notion that opioid-induced hyperalgesia involves complex neuroimmune interactions extending beyond classical neuronal opioid signaling alone.

Supporting the relevance of TNF- α -mediated inflammatory signaling in sensory ganglia, Wei et al. [18] demonstrated that peri-sciatic administration of recombinant TNF- α induced persistent mechanical allodynia accompanied by increased TNF- α and TNFR1 expression in DRG neurons and, to a lesser extent, SGCs. Furthermore, NF- κ B signaling inhibition attenuated both cytokine upregulation and pain behavior, reinforcing the importance of inflammatory neuron–glia interactions in peripheral sensitization.

Beyond cytokine release, inflammatory signaling may also compromise SGCs' homeostatic functions within sensory ganglia. Using an HSV-1-induced herpetic neuralgia model, Silva et al. [26] demonstrated that infiltrating macrophages and neutrophils promoted TNF- α -dependent Kir4.1 downregulation in SGCs, which was associated with neuronal hyperexcitability and mechanical allodynia. These findings further support the idea that SGC dysfunction contributes directly to peripheral sensitization maintenance under inflammatory conditions.

SGC activation has also been associated with stress-related chronic pain conditions. Zhang and Standifer [28] demonstrated increased GFAP expression and enhanced nociceptin/orphanin FQ signaling in sensory ganglia in a combined PTSD–headache pain model, suggesting that traumatic stress may further potentiate glial-mediated nociceptive sensitization.

Purinergic signaling likewise emerged as a recurrent pathway associated with SGC activation in chronic pain. In visceral pain models, P2X7 signaling inhibition reduced neuroinflammatory responses and attenuated pain-related behaviors [30]. Considering the established role of extracellular ATP in neuron–glia communication, these findings suggest that ATP-mediated SGC activation may contribute to peripheral sensitization amplification and inflammatory signaling maintenance within sensory ganglia. Although direct interactions between purinergic pathways and opioid signaling remain insufficiently

characterized, the convergence of these mechanisms supports a relevant modulatory role for SGCs in chronic pain.

Recent evidence further suggests that transcriptional regulation within SGCs may contribute to neuropathic pain maintenance. Yuan et al. [34] demonstrated that TFAP2A upregulation increased Grin1/NR1 expression and inflammatory cytokine production in SGCs following spinal nerve ligation, contributing to neuronal hyperexcitability and persistent nociceptive sensitization.

Collectively, these studies suggest that SGCs may function as active neuroimmune modulators that shape opioid responsiveness through cytokine release, chemokine signaling, and neuron–glia communication. However, most currently available evidence is based on indirect markers of glial activation and experimental animal models. As such, the precise molecular interactions between neurons and SGCs during opioid exposure remain incompletely understood and require further investigation.

More recently, non-opioid mechanisms involving neuron–glia stress response pathways have also emerged as potential therapeutic targets. Yousuf et al. [32] demonstrated that σ 2R/TMEM97 signaling modulation reduced neuropathic pain and inhibited integrated stress response pathways in sensory neurons. Interestingly, σ 2R/TMEM97 expression was also identified in human nociceptors and SGCs, reinforcing the growing translational relevance of glial-associated signaling pathways in chronic pain modulation.

Recent human DRG transcriptomic and in situ hybridization studies further support the translational relevance of neuron–glial opioid signaling. Staedtler et al. [33] identified distinct nociceptive neuronal populations based on OPRM1 expression and demonstrated predominant OPRK1 expression in SGCs within human DRG tissue. These findings reinforce the possibility that SGCs may directly participate in opioid-related modulation in humans, extending observations previously described predominantly in experimental animal models.

Persistent SGC activation and their interactions with receptor-mediated pathways have profound implications for opioid tolerance and dependence. As SGCs are persistently activated [17,19,20], they maintain a neuroinflammatory environment that diminishes opioids' effectiveness. This reduction in efficacy leads to a need for further opioids to achieve the same level of pain relief, accelerating the development of tolerance.

Studies exploring interventions that target these glial pathways offer promising strategies for mitigating opioid tolerance and dependence. For example, the use of CXCR4 antagonists has been shown to reduce the neuroinflammatory response mediated by SGCs, preserving opioids' analgesic efficacy. Similarly, antioxidant treatments such as NAC have been shown to counteract oxidative stress and subsequent MMP-9 release from neurons, preventing SGC activation and maintaining opioid receptor sensitivity. These findings suggest that targeting the specific pathways involved in SGC activation could be a viable approach to improving opioid pain management and reducing the risks associated with long-term opioid use [21,22,25].

Despite growing evidence supporting the role of SGCs in opioid tolerance, several limitations remain. A major challenge is the heterogeneity of experimental pain models, which differ in their underlying mechanisms and may influence SGC activation pathways in different ways. Furthermore, most studies focus on acute or short-term opioid exposure, whereas the long-term effects of chronic opioid use on SGC biology are still poorly understood. Another critical gap lies in the limited exploration of multicellular interactions within the neuroimmune axis. Crosstalk between SGCs and other glial populations, such as microglia and astrocytes, as well as immune cells, including macrophages and T lymphocytes, remains insufficiently characterized.

4.3. Distinguishing Direct from Indirect Evidence of SGCs' Involvement in Opioid Pathways

Direct and indirect evidence associating SGCs with opioid mechanisms must be differentiated and interpreted accordingly. Direct evidence arises from studies that demonstrate SGC activation through increased GFAP immunoreactivity, co-localization of different cell markers, and functional consequences of SGC–neuron interactions using specific cell markers. These include a) morphine-induced ERK1/2 phosphorylation in SGCs alongside neurons in the DRG [31]; b) gap-junction-dependent communication between activated SGCs and neurons, contributing to opioid-induced hyperalgesia [23]; c) MMP-9-mediated SGC activation leading to IL-1 β release, which attenuates morphine analgesia [22,25]; and d) predominant OPRK1 expression in SGCs in human DRG tissues [33]. Indirect evidence arises from studies that infer SGC involvement in opioid neurotransmission from increased expression of inflammatory cytokines, chemokine receptor signaling (e.g., CCR2/CCR5, CCR3, CXCR4), or altered ion channel function in whole DRG tissues under opioid exposure or pain conditions without clearly differentiating SGCs, neurons, and immune cells [17–21,24,26–30,32,34,35].

4.4. Impact of the Heterogeneity of Pain Models in the Included Studies

The considerable heterogeneity across the included studies, encompassing diverse pain types (e.g., neuropathic, opioid-induced hyperalgesia, cancer-related pain, postoperative pain, visceral pain, and acute herpetic neuralgia) and 14 distinct animal models, limits comparison and generalization. Despite this variability, SGC activation emerged as a consistent feature across pain phenotypes, characterized by the release of inflammatory cytokines, altered ion channel function, and increased GFAP expression. However, methodological diversity complicates interpretation, requiring cautious evaluation when extrapolating to specific pain conditions or drawing conclusions regarding interactions between SGCs and the opioid system. The substantial methodological variability among included studies, combined with the predominance of preclinical models, limits the generalizability of findings.

4.5. Methodological Limitations and Strengths of the Included Studies

According to our evaluation, most studies ($n = 13$; 68.4%) exhibited low risk of selection bias, adopting adequate procedures to guarantee allocation and randomization. They also exhibited low risk of detection bias, indicating that adequate procedures for research blinding were implemented in most ($n = 16$; 84.2%); low risk of attrition bias ($n = 14$; 73.7%), indicating appropriate exclusion and dropout documentation; and high risk of reporting bias ($n = 11$; 57.9%), suggesting that the expected outcomes were not reported or not clearly found in most studies.

Some features that impact reproducibility must be considered when evaluating the findings, including (a) lack of power calculation [17–28]; (b) experiments only conducted on male subjects without plausible and/or clear justification [17–31,34,35]; (c) application of non-specific pharmacological tools without genetic validation [19–21,25,27,29,30]; (d) use of structural glial markers (e.g., Iba1 in cases of resident macrophages and GFAP in cases of SGCs) as evidence of functional cell activation without causal validation [22,24,26,28,31]; and (e) whole-tissue analysis, preventing the identification of cellular and molecular changes [17,18,20,25].

On the other hand, several of the included studies were strengthened by the use of advanced tools, such as chemogenetic cell targeting [31], selective scFv antibodies [35], and highly selective pharmacological ligands [32].

4.6. Perspectives

Future research should prioritize investigating unexplored pathways and molecules that may be involved in SGC activation, as well as their interactions with opioid mechanisms. For example, in addition to MMP-9, examining the role of MMP-2 in SGC activation could yield new insights. Similarly, exploring neurotrophic factors such as BDNF may reveal how SGCs influence neuronal plasticity and pain modulation during opioid exposure. Investigating epigenetic modifications in SGCs, particularly in the context of chronic opioid use and its effects on gene expression, represents another promising avenue for research. Additionally, the endocannabinoid system, known for its anti-inflammatory properties and interactions with opioids, could be relevant to SGC function [133]. Advanced techniques such as single-cell RNA sequencing could help to clarify the heterogeneity of SGCs [134], while in vivo imaging methods like two-photon microscopy [135] could provide real-time observations of SGC–neuron interactions. In addition, more human translational studies are necessary to validate preclinical findings, as evidenced by the identification of OPRK1 expression in human DRG tissues [33], a pattern that may differ from that observed in rodents. Moreover, the development of selective SGC-targeted therapies, such as gap junction modulators, P2X7 receptor antagonists, or chemokine blockers, could provide novel therapies to modulate SGC activity without interfering with opioid receptor activity, potentially preserving the analgesic effects of opioids while reducing the risk of developing hyperalgesia and tolerance. By pursuing these new directions, future research could significantly enhance our understanding of SGCs in the functioning of opioid pathways and lead to more effective therapeutic strategies.

5. Conclusions

This systematic review underscored the crucial yet often overlooked role of SGCs in modulating chronic pain and opioid pathways. To the best of our knowledge, this is the first systematic review to focus specifically on SGCs within the context of opioid modulation. Our synthesis of the recent literature shows that, while significant progress has been made in understanding the role of microglia in pain modulation, SGC involvement is increasingly being recognized. Although key players in SGC activation, including MMP-9, CXCR4, TLR2, P2X7 receptors, and the release of pro-inflammatory cytokines, such as IL-1 β and TNF- α , have been identified, a vast array of other cellular pathways remains to be explored. Furthermore, investigating the specific role of SGCs presents significant challenges due to their highly plastic nature; these cells can rapidly alter their properties in vitro, making it difficult to accurately assess their functions under controlled conditions. Some limitations of the current study must be acknowledged, including the substantial heterogeneity in experimental models, differences in outcome measures, and differences in the methodological approaches across the 19 included studies, which limits our ability to draw definitive conclusions. Despite substantial advances in understanding SGC-associated neuroimmune signaling, the precise mechanisms through which these cells modulate opioid responsiveness remain poorly understood, highlighting the need for more studies using standardized methodologies, in addition to refined translational and cell-specific approaches.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/neuroglia7030026/s1>; Complete assessment of the included studies, including the detailed risk-of-bias evaluation using the OHAT Risk of Bias Tool; PRISMA 2020 Checklist: Completed checklist for systematic reviews.

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