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REVIEW

Multifaceted Astrocyte-Neuron Cross-Talk in Neuropathic Pain: Potential Mechanisms and Functional Implications

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Abstract: Neuropathic pain is a prevalent and debilitating chronic condition with complex and incompletely understood mechanisms. Growing evidence has uncovered astrocytes as active and dynamic regulators in both the initiation and persistence of neuropathic pain. Beyond their classical supportive roles, astrocytes undergo profound morphological and functional remodeling following nerve injury and engage in extensive bidirectional communication with neurons. Through direct physical contacts, gliotransmitter release, and complex intercellular signaling networks, astrocytes critically shape synaptic plasticity, neuroinflammatory cascades, and neuronal excitability, ultimately driving maladaptive pain processing. In this review, we provide an updated and integrative overview of astrocyte-neuron cross-talk in neuropathic pain, with a particular focus on the molecular and cellular mechanisms by which astrocytic signaling modulates synaptic remodeling and pain sensitization. A deeper understanding of these astrocyte-mediated interactions may open new avenues for the development of precise and targeted therapeutic strategies for neuropathic pain.

Keywords: neuropathic pain, astrocytes, neuron, cross talk, mechanisms

Introduction

Neuropathic pain is a chronic pain condition caused by a lesion or disease of the somatosensory nervous system.[1] Clinically, neuropathic pain is characterized by spontaneous pain, allodynia and hyperalgesia.[2,3] It is frequently accompanied by chronic comorbidities such as depression and anxiety, which profoundly impair quality of life.[4–6] Current therapeutic strategies, including pharmacological treatments and neuromodulation, remain unsatisfactory due to limited efficacy, drug tolerance, and challenges in long-term management, highlighting the urgent need to identify new therapeutic targets and underlying mechanisms.[6–8]

Glial activation represents a fundamental cellular process underpinning the pathophysiology of neuropathic pain.[9] Under physiological conditions, astrocytes in the central nervous system (CNS) are responsible for maintaining ion homeostasis, providing metabolic support, regulating synaptic function, and clearing neurotransmitters, thereby contributing to neural network stability and information processing.[10,11] By forming tripartite synapses with neurons, astrocytes actively participate in the regulation of synaptic plasticity.[12–14] In addition, astrocytes influence synaptic plasticity by releasing modulators such as D-serine and ATP, and they sustain neuronal metabolic demands by supplying lactate via monocarboxylate transporters.[15,16] However, following nerve injury or under chronic pain conditions, astrocytes become activated and release pro-inflammatory cytokines, exosomes, and metabolites, which modulate synaptic transmission, neuronal excitability, and network remodeling, thereby promoting the propagation and maintenance of pain signaling.[17,18] Intriguingly, a recent study demonstrated that targeted activation of astrocytes in the primary somatosensory cortex reversed mechanical hypersensitivity by inducing synaptic plasticity and reducing aberrant synapse formation after injury, leading to long-lasting pain relief.[19] In contrast, another study in a diabetic neuropathic pain model revealed that activation of motor cortex astrocytes enhanced neuronal

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excitability via the release of inflammatory mediators, thereby facilitating pain maintenance.[20] These findings suggest a bidirectional role of astrocytes in pain regulation: depending on brain region and mode of activation, astrocytes may exert analgesic effects under certain conditions or exacerbate pain hypersensitivity in pathological states.

Astrocyte-neuron interactions are reciprocal and dynamic, encompassing neurotransmitter regulation, inflammatory signaling, metabolic support, synaptic plasticity modulation, and ion homeostasis. Astrocytes maintain neuronal hyperexcitability via these mechanisms, driving the progression of nociceptive sensitivity.[21,22] Deciphering the diverse forms of intercellular communication is crucial for understanding the underlying pathological processes. Here, we review current insights into these interactions, examine their regulatory mechanisms, and evaluate their potential as targets for precision therapies.

Potential Mechanisms of Astrocyte-Neuron Crosstalk in Neuropathic Pain

Direct Astrocyte-Neuron Interactions

Astrocytes form direct interactions with neurons through the tripartite synapse, which comprises the presynaptic terminal, postsynaptic dendritic spine, synaptic cleft, and perisynaptic astrocytic processes (PAPs).[23,24] Unlike conventional bidirectional communication between pre- and postsynaptic neurons, astrocytes detect synaptic activity and actively modulate synaptic transmission through the release of gliotransmitters and regulation of ionic homeostasis.[25] In addition, astrocytic processes tightly enwrap synapses, providing mechanical support to synaptic structures, reducing spatial drift of synaptic sites, and enhancing long-term synaptic stability.[12] Astrocytes, along with perineuronal nets, create a physical scaffold that constrains neurotransmitter spread, optimizes synaptic signaling accuracy, reduces neural circuit interference, and stabilizes local synaptic function.[26] Baldwin et al demonstrated that astrocytes rely on hepatocyte cell adhesion molecule-mediated interactions to compete for neuronal synaptic territories and regulate their morphogenesis and gap junction coupling.[27] In spinal cord injury models, hyperreflexia has been closely associated with increased formation of tripartite synapses involving the astrocytic glutamate transporter (GLT-1) and neuronal PSD-95, suggesting that astrocytes promote central hyperexcitability by regulating synaptic plasticity.[28] In a trigeminal nerve chronic constriction injury model, PAPs in the dorsal medullary horn were markedly elevated, exhibiting enhanced envelopment of presynaptic terminals and postsynaptic dendrites.[29] Via tripartite synapses, astrocytes engage directly with neurons to sense and fine-tune synaptic activity, preserve structural integrity, and maintain precise signal transmission. Astrocytic control via tripartite synapses is crucial for synaptic homeostasis, and its disruption drives neuropathic pain.

Cytokine and Chemokines

Astrocyte activation in the spinal cord and brain is accompanied by the release of pro-inflammatory cytokines that critically modulate neuronal excitability and synaptic plasticity (Table 1). Among these, IL-1β is a key inflammatory mediator that not only enhances excitatory glutamatergic synaptic transmission by binding to IL-1 receptors on neuronal surfaces, but also induces phosphorylation of NMDARs in spinal neurons, thereby amplifying synaptic transmission and pain signaling.[30] In the motor cortex, activated astrocytes release TNF-α and IL-1β, which in turn enhance the excitability of neurons within the same region, contributing to the modulation and exacerbation of diabetic neuropathic pain.[20] Moreover, IL-6 can promote astrocyte activation via the JAK2/STAT3 signaling axis, enhance neuronal electrical excitability, and maintain central sensitization under conditions of spinal cord injury or chronic inflammatory pain.[31,32]

Other inflammatory mediators also play a role. For instance, IL-17 enhances CaMKII/CREB activity in spinal neurons, modulating synaptic transmission and sustaining chronic pain induced by chemotherapy or peripheral nerve injury.[50] IFN-γ activates astrocytes and increases neuronal activity in trigeminal nerve injury models.[45] Nerve injury can epigenetically downregulate miR-214-3p in astrocytes, leading to upregulation of secreted colony-stimulating factor-1 (CSF-1), which enhances neuronal excitability and exacerbates neuropathic pain.[51] Furthermore, the IL-33/ST2 signaling pathway in the spinal cord promotes neuropathic pain development through a dual mechanism involving neuronal CaMKII–CREB and astrocytic JAK2–STAT3 pathways.[44]

Similarly, astrocytes release chemokines, including CXCL1 and CCL2. These molecules act on neuronal receptors CXCR2 and CCR2, activating downstream signaling and enhancing neuronal excitability in pain pathways.[56] For example,

Table 1 Potential Cytokine and Chemokines Mechanisms in Different Neuropathic Pain Models

Potential Mechanisms	Model	Molecule	Source Cell	Target Cell	Expression	Signaling Pathway	Bio-Function	Tissue	Species	Ref
Chemokine	SNL	CXCL13	Neurons	Astrocytes	Increased	ERK signaling pathway	Following nerve injury, upregulation of CBX2 in spinal neurons enhances neuronal and astrocytic hyperactivity via the ERK signaling pathway and increases neuronal CXCL13 expression. Elevated CXCL13 further drives astrocyte activation, ultimately contributing to the development of neuropathic pain.	Spinal cord	Male C57BL/6J mice	[33]
Chemokine	SNL	CXCL1	Astrocytes	Neurons	Upregulated	CXCL1-CXCR2 signaling pathway, c-JNK activation pathway	Spinal astrocytes release CXCL1 through the JNK pathway, which activates CXCR2 receptors on SDH neurons and consequently enhances neuronal excitability.	Spinal cord	Male ICR mice	[34]
Chemokine	LDH	CCL2	Astrocytes	Neurons	Increased	CCL2/CCR2 signaling pathway	CCL2/CCR2 signaling contributes to pain maintenance through neuroinflammation and central sensitization	Spinal cord	Male SD rats	[35]
Chemokine	CCI	CCL2, CCL7	Astrocytes	Neurons	Increased	CCL2/CCR2 and CCL7/CCR2 signaling pathways	After nerve injury, activation of spinal microglia and astrocytes leads to the release of CCL2 and CCL7, which not only drive neuropathic pain development but also diminish the analgesic efficacy of opioids such as morphine and buprenorphine.	Spinal cord	Male Albino Swiss mice	[36]
Chemokine	SNL	CCL7	Neurons	Astrocytes	Increased	/	Following nerve injury, neuronal CCL7 acts on astrocytes to promote their proliferation and activation, representing a key mechanism underlying neuropathic pain development.	Spinal cord	Male SD rats	[37]
Chemokine	CCI	CXCL12	Neurons, astrocytes, and microglia	Neurons, astrocytes, and microglia	Increased	CXCL12/ CXCR4-NLRP3 inflammasome axis	After nerve injury, CXCL12 is produced and released by neurons, astrocytes, and microglia in the SDH. Acting on CXCR4 receptors on these cells, it activates the NLRP3 inflammasome, triggering IL-1β and IL-18 release and thereby promoting neuroinflammation and neuropathic pain.	Spinal Cord	Male SD rats	[38]
Chemokine	CIPN	CXCL1	Astrocytes	Neurons	Increased	CXCL1/CXCR2 signaling pathway	Vincristine induces astrocytic CXCL1 release through the NF-κB pathway, which in turn activates neuronal CXCR2 receptors and contributes to neuropathic pain.	Spinal Cord	Male ICR mice	[39]
Chemokine	SNL	CXCL10	Astrocytes	Neurons	Increased	CXCR3-CXCL10 signaling pathway	Astrocyte-derived CXCL10 activates neuronal CXCR3, enhancing excitatory synaptic transmission and thereby contributing to the maintenance of neuropathic pain.	Spinal Cord	Male C57BL/6 mice	[40]
Chemokine	DNP	CXCR4 and CX43	Neurons and Astrocytes	Neurons and Astrocytes	Increased	CXCR4/CX43 signaling pathway	CXCR4 and CX43 are upregulated in both neurons and astrocytes, and their interaction increases neuronal excitability and disrupts astrocytic function, thereby inducing and sustaining diabetic neuropathic pain.	SDH	Male SD rats	[41]
Chemokine	PHN	CCL5	/	/	Increased	CCL5/CCR5 signaling pathway	HSV-1 infection upregulates CCL5 and its receptor CCR5 in the DRG and spinal cord, eliciting an immune response and promoting the release of inflammatory cytokines.	DRG, Spinal Cord	Male C57BL/6J mice	[42]
Chemokine	SNL	CXCL13	Neurons	Astrocytes	Increased	CXCL13/ CXCR5/ERK signaling pathway	Neuronal CXCL13 activates astrocytes through CXCR5, promoting neuropathic pain by driving astrocyte activation and inflammatory responses.	Spinal Cord	ICR mice and C57BL/6mice	[43]
Cytokine	SNI	IL-33	Neurons & Astrocytes	Neurons &Astrocytes	Increased	1. Neuronal CaMKII-CREB cascade 2. Astroglial JAK2-STAT3 cascade	The IL-33/ST2 signaling in the spinal cord jointly promotes the occurrence and development of neuropathic pain by activating specific signaling pathways in neurons and astrocytes respectively.	Spinal cord	Male BALB/c mice	[44]

(*Continued*)

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Table 1 (Continued).

Potential Mechanisms	Model	Molecule	Source Cell	Target Cell	Expression	Signaling Pathway	Bio-Function	Tissue	Species	Ref
Cytokine	IONI	IFN-γ	Astrocytes	Neuron	Increased	IFN-γ signaling pathway	IFN-γ signaling in spinal trigeminal caudal subnucleus astrocytes mediates orofacial neuropathic pain following trigeminal nerve injury by enhancing neuronal activity and lowering pain thresholds.	Spinal trigeminal caudal subnucleus, Vc	Male SD rats	[45]
Cytokine	DNP	TNF-α, IL-1β	Astrocytes	Neurons	Increased	/	In the motor cortex, activated astrocytes release pro-inflammatory cytokines, which in turn increase the excitability of neurons within the same region, thereby regulating and exacerbating diabetic neuropathic pain.	MCx	Male SD rats	[20]
Cytokine	SCI	BDNF	Astrocytes	Astrocytes	Increased	/	Upregulation of the TrkB. T1 receptor on astrocytes drives their proliferation and migration upon BDNF binding, leading to gliosis and dysfunction.	Spinal Cord	Male C57BL/6J mice	[46]
Cytokine	PHN	IL-1β	Astrocytes	Neurons	Increased	/	Activated spinal astrocytes produce NO and IL-1β, inducing NMDAR phosphorylation in SDH neurons, strengthening pain transmission and contributing to mechanical allodynia	Spinal cord	Male Wistar rats	[47]
Cytokine	CCI	IFN-γ	Neurons	Astrocytes	Increased	IL-12/IFN-γ/ CXCL10 pathway	IL-12/IL-18–stimulated spinal neurons produce IFN-γ, which upregulates CXCL10 in neurons and astrocytes, driving neuron–astrocyte crosstalk and neuropathic pain.	Spinal Cord	Male and female SD rats	[48]
Cytokine	CIPN	IL-17	Astrocytes	Neurons	Increased	/	IL-17 enhances EPSCs, suppresses IPSCs and GABA-induced currents in somatostatin-expressing neurons, and induces neuronal hyperexcitability in nociceptive sensory neurons	Spinal cord, DRG	Male C57BL/6J mice	[49]
Cytokine	SNL	IL-17A	Astrocytes	Neurons	Increased	CaMKII/CREB signaling pathway	Astrocytic IL-17A maintains neuropathic pain through CaMKII/CREB signaling in spinal neurons.	Spinal cord	Male C57BL/6 mice	[50]
Cytokine	SNL	CSF1	Astrocytes	Neurons	Increased	DNMT3a/miR-214-3p/CSF1 pathway	DNMT3a-mediated epigenetic suppression of miR-214-3p enhanced CSF1 production in astrocytes, which subsequently induced neuroinflammation, neuronal hyperexcitability, glutamatergic receptor upregulation, and pain behavior	Spinal cord	Male SD rats	[51]
Cytokine	DNP	IL-1β	Astrocytes	Neurons	Increased	IL-1β/NMDAR pathway	Activated astrocytes increase IL-1β expression, inducing NMDAR phosphorylation in SDH neurons to enhance pain transmission	Spinal cord	C57BLKS db/db mice and C57BL6 mice	[30]
Cytokine	CCI	TNF-α, IL-1	Astrocytes	Neurons	Increased	TNFR1/IL-1R / NMDAR phosphorylation pathway	Glial cytokines couple glial hyperactivation with NMDAR function, enhancing descending pain facilitation	RVM	Male SD rats	[52]
Cytokine	CIPN	IL-1β	Astrocytes	Neurons	Increased	/	Activated astrocytes increase IL-1β, inducing NMDAR phosphorylation to strengthen pain transmission	Spinal cord	Male SD rats	[53]
Cytokine	CIPN	IL-1α	Neurons	Astrocytes	Increased	/	Neuronal alarmin IL-1α evokes astrocyte-mediated protective signals and reduces endogenous glutamate release in the spinal cord, thereby effectively ameliorating chemotherapy-induced neuropathic pain.	Spinal Cord, Cortical Neurons	Male SD rats	[54]
Cytokine	SCI	IL-6	Astrocytes	Neurons	Increased	IL-6/JAK2/STAT3 Pathway	The IL-6/JAK2/STAT3 signaling axis is activated in astrocytes, promoting their activation and thereby mediating and maintaining neuropathic pain.	L4-5 Dorsal Horn	Male SD rats	[31]
Cytokine	SNI	IL-17	Astrocytes	Neurons	Increased	IL-17/IL-17RA Signaling Pathway	Spinal astrocyte-secreted IL-17, by binding to IL-17RA on neurons, enhances the excitatory activity of spinal dorsal neurons, facilitates C-fiber evoked field potentials LTP	SDH	Male C57BL/6 J mice	[55]

Note: "/" means not mentioned in the article.

Abbreviations: SNL, Spinal nerve ligation; LDH, Lumbar disc herniation; CCI, Chronic constriction injury; SNL, Spinal nerve ligation; CIPN, Chemotherapy induced peripheral neuropathy; DNP, Diabetic neuropathic pain; PHN, Postherpetic neuralgia; SNI, Spared nerve injury; IONI, Infraorbital Nerve Injury; CXCL, C-X-C Motif Chemokine Ligand; CCL, C-C Motif Chemokine Ligand; CXCR, C-X-C Motif Chemokine Receptor; IL, Interleukin; IFN-γ, Interferon gamma; TNF-α, tumor necrosis factor; BDNF, Brain-Derived Neurotrophic Factor; CSF1, Colony Stimulating Factor 1; NLRP3, NOD-like receptor protein 3; ERK, Extracellular Signal-Regulated Kinase; CREB, cAMP Response Element-Binding Protein; CaMKII, Calcium/Calmodulin-Dependent Protein Kinase II; STAT3, Signal Transducer And Activator Of Transcription 3; DNMT3a, DNA Methyltransferase 3 alpha; NMDAR, N-methyl-D-aspartic acid receptor; SD, Sprague-Dawley; DRG, dorsal root ganglia; LTP, Long-term potentiation.

CXCL1 is upregulated and released from spinal astrocytes, and acts on CXCR2-expressing spinal neurons to activate ERK and CREB signaling, enhance neuronal excitability, and induce immediate early gene expression, thereby promoting central sensitization and persistent pain.[34,57] Following inflammation or nerve injury, activated spinal astrocytes secrete CCL2, which binds to CCR2 expressed on neurons, modulating synaptic transmission and enhancing NMDA receptor function, thus facilitating central sensitization.[58,59] In addition, CXCL10 expression is upregulated in spinal neurons and astrocytes after nerve injury. CXCL10 enhances spontaneous excitatory postsynaptic currents and potentiates NMDA- and AMPA-induced currents in spinal neurons, further amplifying neuronal responsiveness to pain stimuli.[40] Collectively, Cytokines and chemokines mediate neuron-astrocyte signaling, forming a positive feedback loop that enhances neuronal excitability and sustains neuropathic pain.

Extracellular Vesicles

Extracellular vesicles(EVs), particularly exosomes, are key mediators of intercellular communication. Exosomes are nanoscale vesicles, approximately 30–150 nm in diameter, capable of carrying diverse bioactive cargos, including miRNAs, mRNAs, proteins, and lipids, which can be internalized by target cells via endocytosis to modulate gene expression and cellular functions. While studies of exosomes in neuropathic pain remain scarce, accumulating evidence highlights their roles in various neurodegenerative conditions.[60]

miRNAs packaged within astrocyte-derived exosomes have emerged as critical regulators of neuronal gene expression and synaptic plasticity. For instance, exosomes enriched in miR-26a-5p exert neuroprotective effects by inhibiting neuronal apoptosis and promoting dendritic development.[61] Mechanistically, miR-26a-5p targets neural cell adhesion molecule and activates the AKT/GSK3-β/CRMP2 signaling pathway, thereby enhancing neuronal function.[61] Similarly, miR-378a-5p carried by astrocyte-derived exosomes mitigates NLRP3-mediated pyroptosis and neuroinflammation, conferring neuroprotection in cerebral ischemia.[62] Neurons also release exosomes to transfer miR-124-3p to microglia and astrocytes, suppressing M1 microglia and A1 astrocyte activation through modulation of MYH9 and the PI3K/AKT/NF-κB signaling axis, which facilitates functional recovery following spinal cord injury.[63]

Beyond miRNAs, exosomes transport specific proteins that critically regulate neuronal functions. Astrocytic processes release exosomes containing neuroglobins, contributing to noncanonical CNS signaling and selectively targeting neurons to exert protective effects.[64] Following mild cortical spreading depolarization, stressed neurons release small HMGB1-enriched exosomes that are internalized by astrocytic processes, activating NF-κB p65 signaling and eliciting inflammatory responses.[65] Interestingly, astrocyte-derived exosomes (ADEVs) exhibit stimulus-dependent protein cargos: ATP or IL-10 stimulation enriches proteins promoting neurite outgrowth, dendritic branching, synaptic transmission, and neuronal survival, whereas IL-1β-stimulated ADEVs are enriched in proteins that modulate peripheral immune responses and recruit immune cells into the CNS.[66] Collectively, these findings highlight exosomes as key mediators of astrocyte-neuron communication and suggest their potential as therapeutic targets for chronic pain intervention.

Synapse-Associated Molecules

Astrocytes orchestrate neuronal plasticity via synapse-associated molecules, thereby influencing synaptic transmission and promoting neuropathic pain (Table 2). D-serine, a key NMDAR co-agonist released by astrocytes, enhances excitatory synaptic transmission.[15,67,68] Members of the Hevin/SPARC protein family exert opposing effects on synaptic remodeling: Hevin promotes postsynaptic dendritic spine formation, potentially enhancing nociceptive signaling, whereas SPARC inhibits synaptic remodeling, reducing pain hypersensitivity.[69] Astrocyte-derived Hevin has been shown to sustain neuropathic and inflammatory pain by upregulating spinal GluN2B expression.[70] In addition, astrocytes secrete Chordin-like 1, which promotes synapse maturation and constrains plasticity by increasing GluA2 receptor expression at synapses.[71]

Matrix metalloproteinases (MMPs) are key regulators of the extracellular synaptic matrix and play pivotal roles in neuropathic pain. MMP-9 degrades chondroitin sulfate proteoglycans (CSPGs), influencing synaptic stability and facilitating synaptic remodeling.[77] CSPGs form perisynaptic barriers that limit synaptic plasticity and maintain synaptic stability.[78] Abnormal CSPG accumulation after nerve injury may impede repair, whereas its degradation promotes plasticity and modulates pain signal transmission.[79] Furthermore, the Sema3A/Neuropilin-1 signaling pathway regulates synaptic plasticity, with astrocyte-derived Sema3A mediating axonal retraction and synaptic functional changes via Neuropilin-1 receptor.[79]

Table 2 Potential Synapse-Associated Molecules Mechanisms in Different Neuropathic Pain Models

Potential Mechanisms	Model	Molecule	Source cell	Target Cell	Expression	Signaling Pathway	Bio-Function	Tissue	Species	Ref
Synaptic modifying molecule	SNL	Cx43	Neurons	Astrocytes	Decreased	Glutamate signaling	Downregulation of spinal astrocytic Cx43 leads to decreased GLT-1 expression, reduced glutamate clearance, increased glutamatergic neurotransmission, and the maintenance of neuropathic pain.	Lumbar SDH	Male ddy mice	[72]
Synaptic modifying molecule	CCI	Cx43	Astrocytes	Neurons	Increased	σ1R signaling pathway	Targeting σ1R attenuates astrocyte and microglia activation, normalizes Cx43 levels to limit deleterious intercellular communication, and confers neuroprotection, thereby alleviating neuropathic pain.	DRG	Male SD rats	[73]
Synaptic modifying molecule	CIPN	Cx43	Astrocytes	Astrocytes	Increased	/	Spinal astrocyte gap junctions contribute to the induction of oxaliplatin-induced neuropathic pain but do not participate in its maintenance.	SDH	Male SD rats	[74]
Synaptic modifying molecule	SCI	Cx43	Astrocytes	Astrocytes	Increased	Sigma-1 receptor mediated pathway	Astrocyte σ1R signaling drives Cx43-mediated astrocyte–neuron communication, promoting the induction of bilateral below-level mechanical allodynia after spinal cord injury.	Lumbar SDH	Male ICR mice	[75]
Synaptic modifying molecule	SNI	Cx36, Cx43	Neurons	Glial cells	Increased	TRESK downregulation-mediated pathway	TRESK downregulation contributes to the pathogenesis of neuropathic pain by enhancing synaptic transmission and activating spinal glial cells.	Spinal cord	Male SD rats	[76]
Synaptic modifying molecule	CCI	Hevin	Astrocytes	Neurons	Increased	NMDA receptor signaling	Astrocyte-secreted Hevin critically maintains chronic pain by potentiating spinal GluN2B-containing NMDA receptor signaling	L4–L5 spinal cord	Hevin KO mice	[70]

Notes: "/" means not mentioned in the article.

Abbreviations: SNL, Spinal nerve ligation; LDH, Lumbar disc herniation; CCI, Chronic constriction injury; SNL, Spinal nerve ligation; SCI, chronic constriction injury of the sciatic nerve; CIPN, Chemotherapy induced peripheral neuropathy; DNP, Diabetic neuropathic pain; PHN, Postherpetic neuralgia; SNI, Spared nerve injury; Cx43, Connexin 43; TRESK, TWIK-Related Spinal Cord Potassium Channel; NMDAR, N-methyl-D-aspartic acid receptor; GLT-1, Glutamate transporter-1; SDH, Spinal dorsal horn; DRG, dorsal root ganglia; SD, Sprague-Dawley.

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Connexins (Cxs) modulate astrocyte–neuron interactions and inter-astrocytic coupling, driving synaptic abnormalities and pain sensitization. Neuronal potassium channel activity downregulation leads to upregulation of neuronal Cx36 and astrocytic Cx43, enhancing synaptic transmission and glial activation.[76] In chemotherapy-induced neuropathic pain, increased astrocytic Cx43 mediates aberrant intercellular communication, facilitating pain hypersensitivity.[74] Following spinal cord injury, Sigma-1 Receptor activation further elevates astrocytic Cx43 expression and coupling, accelerating central sensitization and mechanical allodynia.[75] Collectively, astrocytes influence neuronal synaptic plasticity and excitatory transmission through the secretion and regulation of multiple synapse-associated molecules.

Ion Homeostasis

Astrocytes engage in bidirectional interactions with neurons through diverse mechanisms of ionic homeostasis, which play crucial roles in the initiation and maintenance of neuropathic pain[80] (Table 3). Astrocytes regulate extracellular K^+ buffering via Kir4.1 potassium channels, thereby modulating neuronal excitability.[81] In chronic constriction injury models, impaired K^+ channel function in dorsal horn astrocytes increases astrocytic excitability, alters neuronal firing patterns, and enhances neuronal excitability.[82] Aberrant Ca^{2+} signaling also represents a key factor in pain modulation. Astrocytic Ca^{2+} fluctuations directly influence synaptic function and neurotransmitter release, while Ca^{2+} signals mediated via P2Y receptor activation further potentiate pain signal transmission.[83] Notably, electroacupuncture has been reported to modulate Ca^{2+} dynamics in rostral ventromedial medulla astrocytes, activating downstream signaling pathways to achieve analgesic effects.[84]

Astrocytes also modulate neuronal excitability through Na^+/K^+-ATPase. In migraine, Na^+/K^+-ATPase dysfunction leads to elevated extracellular Na^+, concomitant with reduced perisynaptic glutamate transporter density, slowing glutamate clearance, and increasing cortical susceptibility to spreading depolarization, thereby enhancing nociceptive responses to migraine triggers.[94] Astrocytic regulation of Cl^- homeostasis further influences neuronal excitability; impaired Cl^- efflux raises intracellular Cl^- in neurons, weakening GABAergic inhibition and promoting hyperexcitability.[95] Activation of astrocytic BDNF-TrkB signaling downregulates Cl^- extrusion transporters while enhancing the release of pro-inflammatory cytokines and neurotrophic factors, establishing a positive feedback loop that sustains pain signaling.[96] In spared nerve injury models, differential target multiplexed programming of spinal cord stimulation modulates a broader array of ion homeostasis-related proteins compared with low-frequency stimulation. Regulation of proteins controlling Ca^{2+}, Na^+, K^+, and Cl^- homeostasis leads to reduced intracellular Ca^{2+}, enhanced GABAergic inhibition, and restored K^+ and Cl^- balance, thereby reversing ion dysregulation and neuronal hyperexcitability in pain states.[97] Overall, astrocytes regulate neuronal excitability and synaptic transmission via ion homeostasis, critically contributing to the onset and maintenance of chronic pain.

Energy Metabolism

Reciprocal metabolic coupling, via astrocytic lactate and ATP release and mitochondrial transfer, shapes neuronal excitability and perpetuates pain signaling (Table 3). Among these mechanisms, lactate shuttling is particularly critical. During inflammatory pain, astrocytes generate lactate through glycogenolysis and transport it to neurons via monocarboxylate transporters. Lactate serves as an energy substrate, facilitating synaptic plasticity and heightened excitability in spinal neurons, thereby sustaining pain states.[88,98] In the spinal cord, lactate shuttling enhances C-fiber-induced long-term potentiation, exacerbating mechanical hypersensitivity.[87,99] In higher brain regions such as the anterior cingulate cortex and hippocampus, astrocyte-derived lactate modulates synaptic plasticity, augments pain sensitization, and influences pain-associated cognitive and emotional processes.[100,101] ATP also regulates neuronal activity. Astrocyte activation triggers ATP release, which enhances neuronal excitability and pain hypersensitivity, effects that can be reversed upon blockade of ATP receptors.[102] Conversely, dorsal horn neurons in neuropathic pain states release ATP via vesicular nucleotide transporter-mediated vesicular exocytosis, sustaining pain signaling.[93]

Mitochondrial transfer mediated by astrocytes has emerged as a novel form of intercellular communication, essential for maintaining neuronal function and metabolic homeostasis. Although its role in neuropathic pain remains unclear, extensive studies in various neurodegenerative and injury models provide insights. For instance, the Tak1 signaling pathway promotes mitochondrial transfer from astrocytes to hypothalamic proopiomelanocortin neurons, maintaining glucose and cholesterol homeostasis.[103] In Rett Syndrome models, astrocytic mitochondrial dysfunction and excessive reactive oxygen species (ROS) production impair their neuronal support capacity.[104] Acupuncture interventions in acute

Table 3 Potential Ion Homeostasis and Energy Metabolism Mechanisms in Different Neuropathic Pain Models

Potential Mechanisms	Model	Molecule	Source Cell	Target Cell	Expression	Signaling Pathway	Bio-Function	Tissue	Species	Ref
Ion Homeostasis	CCI	K+	Astrocytes	Neurons	Decreased	Potassium ion channel signaling pathway	Decreased spinal astrocytic Kir4.1 expression increases astrocyte excitability, alters the firing patterns of neurons in the dorsal spinal cord, and leads to hyperalgesia.	Dorsal Spinal Cord	Neonatal male and female C57BL/6J mice	[82]
Ion Homeostasis	CIPN	Ca2+	Astrocytes	Neurons	Increased	IP3R2-dependent and non-IP3R2-dependent Ca2+ signaling pathways	Paclitaxel induces astrocytic calcium signaling and neuronal activation in the RVM, contributing to mechanical allodynia, while inhibition of astrocytic calcium activity reproduces the analgesic effects of electroacupuncture.	RVM, spinal cord	Male and female C57BL/6J mice	[84]
Ion Homeostasis	SNL	Ih	Astrocytes	Neuron	Increased	/	Astrocytes modulate neuronal excitability and pain-associated behaviors by altering hyperpolarization-activated current and affecting mechanical withdrawal thresholds	Central Nucleus of Amygdala	Male SD rats	[85]
Energy Metabolism	CCI	VEGF, PKM2	Astrocytes	Neurons	Upregulated	HIF-1α signaling pathway	Fumagillin mitigates neuropathic pain by inhibiting VEGF/ANG2-driven astrocyte–neuron metabolic reprogramming and spinal dorsal horn angiogenesis	SDH	Male wistar rats	[86]
Energy Metabolism	CCI	ANG2, Lactate	Neurons	Astrocytes	Upregulated	HIF-1α signaling pathway	Fumagillin mitigates neuropathic pain by inhibiting VEGF/ANG2-driven astrocyte–neuron metabolic reprogramming and spinal dorsal horn angiogenesis	SDH	Male wistar rats	[86]
Energy Metabolism	HFS	L-lactate	Astrocytes	Neurons	Increased	ERK signaling pathway, Glucocorticoid receptor pathway	Lactate release from astrocytes enhances synaptic transmission, induces LTP, and contributes to mechanical allodynia and pain chronicity	SDH	Male and female SD rats and Aldh1L1-CreERT2 mice	[87]
Energy Metabolism	IONX	Lactate	Astrocytes	Neurons	Increased	Astrocyte-Neuron Lactate Shuttle pathway	ANLS contributes to central sensitization and maintenance of trigeminal neuropathic pain	Vc	Male SD rats	[88]
Energy Metabolism	SNL	GABA	Astrocytes	Neurons	Increased	MAOB pathway, Neuronal K+/Cl- cotransporter pathway	Astrocytic GABA causes tonic neuronal excitation, increases glucose metabolism, and contributes to mechanical allodynia and neuropathic pain	SDH	Male SD rats	[89]
Energy Metabolism	SNL	L-Lactate	Astrocytes	Neurons	Increased	/	Astrocytic L-lactate secretion induced by PACAP activation contributes to nociceptive behaviors through neuronal stimulation	SDH	Male ddY mice, pregnant female ddY mice	[90]
Energy Metabolism	LDH	L-Lactate	Astrocytes	Neurons	Increased	ANLS	Astrocytic L-lactate sensitizes nociceptive transmission by lowering mechanical nociceptive threshold and upregulating neuronal activation markers	SDH	Male ddY mice, C57BL/6 J mice	[91]
Energy Metabolism	SNI	Lactate	Astrocytes	Neurons	Decreased	β2-adrenergic receptor signaling	Lactate released from astrocytes in the dCA1 enhances the excitability of pyramidal neurons and potentiates NMDA receptor-mediated excitatory postsynaptic potentials, thereby alleviating nociceptive sensitization and memory deficits.	Dorsal hippocampal CA1	Male and female SD rats, C57BL/6 mice	[92]
Energy Metabolism	SNI	ATP	Neurons	Astrocytes	Increased	/	Increased VNUT expression in SDH neurons leads to enhanced exocytotic ATP release, raising extracellular ATP levels in the spinal cord. Extracellular ATP activates spinal purinergic receptors, which is a key mechanism underlying neuropathic hypersensitivity.	SDH	Male C57BL/6 Mice	[93]

Notes: "/" means not mentioned in the article.

Abbreviations: CCI, Chronic constriction injury; CIPN, Chemotherapy induced peripheral neuropathy; SNL, Spinal nerve ligation; HFS, High-frequency stimulation; IONX, infraorbital nerve transection;SNL, Spinal nerve ligation; LDH, Lumbar disc herniation; VEGF, Vascular Endothelial Growth Factor; PKM2, Pyruvate Kinase M2; ANG2, Angiopoietin-2; GABA, Gamma-Aminobutyric Acid; ATP, Adenosine Triphosphate; HIF-1α, Hypoxia-Inducible Factor 1 alpha; ERK, Extracellular Signal-Regulated Kinase; MAOB, Monoamine oxidase type B; ANLS, Astrocyte-neuron lactate shuttle; RVM, Rostral ventromedial medulla; LTP, Long-term potentiation; SDH, Spinal dorsal horn; DRG, dorsal root ganglia; SD, Sprague-Dawley.

stroke models enhance astrocyte-to-neuron mitochondrial transfer, conferring neuroprotection.[105] Recent studies also show that LRP1-mediated mitochondrial transfer from astrocytes mitigates cerebral ischemic injury through inhibition of ADP-ribosylation factor 1 myristoylation,[106] and reactive astrocytes with abnormal mitochondrial dynamics are closely associated with neuronal damage in multiple pathological conditions.[107] These findings suggest that astrocytic mitochondrial transfer can be protective or harmful depending on context and may modulate neuronal metabolism, synaptic plasticity, and ROS to influence pain pathways, warranting further study.

Neurotransmitter Regulation

Astrocytes regulate neurotransmitter signaling to sustain neuronal excitability and modulate pain (Table 4). In key pain-processing regions such as the spinal dorsal horn and hypothalamus, astrocytes maintain the balance of excitatory and inhibitory synaptic transmission by clearing excess glutamate from the synaptic cleft via GLT-1.[28] When astrocytic function is impaired or GLT-1 expression is downregulated, glutamate clearance is compromised, leading to elevated extracellular glutamate levels, enhanced excitatory synaptic plasticity, and central sensitization, thereby exacerbating chronic pain phenotypes.[108,109] Moreover, astrocytes can sense synaptic glutamate through metabotropic glutamate receptor 5, triggering intracellular Ca^{2+}-dependent responses that further disrupt excitatory signaling.[110]

Beyond glutamate, norepinephrine also participates in astrocyte–neuron cross talk. Norepinephrine released from locus coeruleus neurons in the midbrain acts on astrocytes to suppress pro-inflammatory activation, thereby reducing astrocyte-mediated neuroinflammation, limiting glutamate-driven neuronal hyperexcitability, and alleviating pain transmission.[111] Pharmacological studies indicate that upregulating GLT-1 in astrocytes enhances glutamate clearance, suppresses neuronal hyperexcitability, and significantly improves pain behaviors in spinal cord injury or neuropathic pain models.[131] Together, astrocytes orchestrate neurotransmitter signaling to modulate synaptic transmission and central sensitization.

Conclusions and Future Directions

In this review, we summarized the multifaceted mechanisms by which astrocyte-neuron interactions contribute to the initiation and maintenance of neuropathic pain. These interactions occur both through direct cell-cell contacts and via indirect pathways, including cytokine/chemokine signaling, extracellular vesicle release, synapse-associated molecules, ion homeostasis, energy metabolism, and neurotransmitter regulation (Figure 1). These mechanisms are highly interconnected, collectively shaping central sensitization and synaptic plasticity.

In the central nervous system, astrocytes are not merely supportive cells for neurons but are pivotal regulators of neural network function. Through the formation of tripartite synapses and the envelopment of presynaptic terminals and postsynaptic dendrites by PAPs, astrocytes are capable of sensing neuronal activity and modulating synaptic transmission, thereby contributing to the regulation of synaptic plasticity.[23–25] Via gap junctions and an extensive astrocytic network, they facilitate lateral signal propagation, enabling local neuronal activity to be coordinated across broader neural circuits. In addition, astrocytes provide essential metabolic support, including the release of lactate and ATP as well as mitochondrial transfer, ensuring neuronal energy supply and the maintenance of activity-dependent plasticity.[88,102,103] Astrocytes also play a central role in maintaining ion homeostasis, including Ca^{2+}, K^+, and Cl^-, thereby regulating neuronal excitability and preventing aberrant firing.[81,83,95] Under inflammatory or chronic pain conditions, astrocytes release gliotransmitters, cytokines, and chemokines, participating in bidirectional neuron-glia signaling that amplifies central sensitization and synaptic plasticity.[31,56]

Accumulating evidence suggests that astrocyte-neuron communication in neuropathic pain is mediated by an integrated signaling network rather than independent pathways. Following nerve injury, excessive neuronal activity and the release of neurotransmitters activate astrocytes and trigger multiple downstream responses, including the production of cytokines and chemokines, extracellular vesicles, synapse-associated molecules, and alterations in ion homeostasis and metabolic coupling.[132] Importantly, these pathways exhibit substantial functional crosstalk. For example, astrocyte-derived TNF-α and IL-1β not only directly enhance neuronal excitability but also impair glutamate homeostasis and facilitate NMDA receptor activation, while IL-6 amplifies inflammatory signaling through the JAK2/STAT3 pathway.

These signaling pathways further interact to reinforce maladaptive neuron-astrocyte communication. Extracellular vesicles can propagate inflammatory signals by transferring regulatory miRNAs and proteins, whereas synapse-associated molecules such as Hevin and D-serine directly promote excitatory synaptic remodeling.[69] Meanwhile, disturbances in ion

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Table 4 Potential Neurotransmitter and Other Molecule Mechanisms in Different Neuropathic Pain Models

Potential Mechanisms	Model	Molecule	Source Cell	Target Cell	Expression	Signaling Pathway	Bio-Function	Tissue	Species	Ref
Neurotransmitter	CCI	NE	Neurons	Astrocytes	Increased	α2-adrenergic receptor pathway	Norepinephrine released from LC via α2B receptor inhibits astrocytes by reducing TNF-α and IL-1β and increasing IL-4 and IL-10, ultimately alleviating neuropathic pain	SDH, LC	Male C57/BL6J mice	[111]
Neurotransmitter	SNL	Glutamate	Astrocytes	Neurons	Increased	GLT-1 dependent mechanism	Gabapentin induces glutamate release from astrocytes in the LC to stimulate descending inhibition for pain relief.	LC	Male SD rats	[112]
Neurotransmitter	NRC	Glutamate	Neurons	Astrocytes	Decreased	/	Nerve root-mediated pain is maintained jointly by spinal astrocytic reactivity and neuronal hyperexcitability, which are associated with reduced glutamate uptake by GLT-1.	Spinal cord	Male Holzman rats	[108]
Neurotransmitter	SCI	Glutamate	Neurons	Astrocytes	Decreased	GLT1/FosB pathway	Reduced GLT1 expression leads to dysregulation of glutamate, causing hyperexcitability of dorsal horn neurons and neuropathic pain; restoring GLT1 expression reverses pain behavior and reduces neuronal activation.	Cervical spinal cord	Male C57BL/6 mice	[113]
Neurotransmitter	SNI	Glutamate	Neurons	Astrocytes	Increased	Glutamate signaling	NaHS enhances mechanical and thermal pain thresholds, reduces glutamate levels in the spinal cord, and decreases the discharge frequency of neurons in the S1HL by modulating astrocyte function and enhancing EAAT2 expression.	Spinal cord, S1	Male C57BL/6 mice	[114]
Neurotransmitter	SCI	GLT-1	Astrocytes	Neurons	Increased	/	The increased presence of astrocyte-neuron synaptic complexes is involved in the plasticity-driven progression of chronic spasticity and hyperreflexia following spinal cord injury.	Ventral Horn	Male and female C57BL/6 mice	[28]
Neurotransmitter	CCI	mGluR5	Astrocytes	Neurons	Increased	mGluR5 signaling pathway	Following nerve injury, peripheral astrocytic processes undergo structural reorganization around central synapses, which may be the structural basis for enhancing astrocyte-neuron interaction in neuropathic pain.	Medullary dorsal horn	Male SD rats	[29]
Neurotransmitter	SNL	mGluR5	Astrocytes	Neurons	Increased	mGluR5-Ca^{2+} signaling pathway	Reemerged mGluR5 in astrocytes drives Ca^{2+} signals, upregulates multiple synaptogenic molecules, causes excess excitatory synaptogenesis, and produces persistent alteration of S1 neuronal activity, leading to mechanical allodynia	S1	C57Bl/6 mice	[110]
Neurotransmitter	SNL	NO	Neurons	Astrocytes	Increased	NMDAR-NOS-JNK pathway	Neuronal transmission initiates astrocytic activation-induced neuroinflammation, contributing to neuropathic pain development	SDH	Male SD rats	[115]
Molecule	SNL	δ-opioid	Neurons	Astrocytes	Dysfunction	δ-opioidergic system	Chronic pain causes cortical δ-opioid receptor dysfunction leading to astrogliosis in the cingulate cortex, which contributes to emotional disorders.	Cg	Male C57BL/6J mice	[116]
Molecule	CIPN	IGF-1	Astrocytes	Neurons	Decreased	IGF-1/IGF1R signaling pathway	Fumagillin alleviates chemotherapy-induced pain-like behavior by modulating astrocyte–neuron interactions and suppressing inflammatory markers.	Lumbar spinal cord	Male C57BL/6 mice	[116]
Molecule	SNL	ZnT1	Astrocytes	Neurons	Decreased	BDNF-TrkB-KCC2 cascade reaction	Downregulation of zinc transporter-1 in astrocytes induces tactile allodynia and neuropathic pain by disrupting zinc-dependent astrocyte–neuron signaling, highlighting its role in pain pathophysiology.	Spinal cord	Male ddY mice	[95]
Molecule	OIH	Wnt5a	Neurons	Astrocytes	Activated	Wnt5a-ROR2 signaling pathway	Neuron-derived Wnt5a signaling activates astrocytes, leading to astrogliosis and inflammatory responses, which is crucial for the formation of OIH.	SDH	Male C57BL/6 mice	[117]

Molecule	CIPN	S1P	Neurons	Astrocytes	Increased	S1PR1 signaling pathway	S1PR1 activation engages astrocyte-driven neuroinflammation and alters glutamatergic homeostasis, leading to neuropathic pain.	SDH	Male SD rats and C57BL/6J mice	[118]
Molecule	SNI	RGS2, RGS3, RGS4, RGS7	Astrocytes	Neurons	RGS3 upregulated early; RGS2 and RGS4 decreased later; RGS7 continuously decreased	GPCR signaling pathway	Astrocytic RGS expression constitutes an adaptive mechanism in neuroinflammation and may contribute to the modulation of nociceptive signaling.	Lumbar spinal cord dorsal quadrant	Female SD rats	[119]
Molecule	SCI	17β-estradiol	Astrocytes	Neurons	Increased	MAPK signaling pathway	Estrogen attenuates spinal cord injury–induced neuropathic pain by inhibiting astrocyte activation and the ensuing neuroinflammatory response, highlighting its neuroprotective function.	L4-5 SDH	Male SD rats	[120]
Molecule	SNI	PK2	Astrocytes	Neurons	Increased	GPCR signaling pathway	PC1 regulates pain sensation and inhibits spinal neuronal hypersensitivity, highlighting its role in mitigating neuropathic pain.	Spinal cord	Male CD-1 mice	[121]
Molecule	SNI	pERK	Not applicable	Neurons	Increased	ERK signaling pathway	Insular cortex stimulation regulates neuropathic pain by modulating ERK phosphorylation in neurons, highlighting its role in neuronal signaling and pain modulation.	IC	Male SD rats	[122]
Molecule	CCI	P2X3	Neurons	Astrocytes	Increased	P2X3 purinergic signaling	In the brainstem, neuronal glutamate induces upregulation of P2X3 receptors in astrocytes, which are subsequently activated by neuronal ATP, collectively driving the development of craniofacial neuropathic pain.	Trigeminal Caudal Nucleus	Male SD rats	[123]
Molecule	SCI	UA	Neurons	Astrocytes	Decreased	Purine Salvage Pathway	B9 Alleviates SCI-Induced Mechanical Pain by Inhibiting Cypin and Reducing Uric Acid Production	Spinal Cord	Female C57BL/6 mice	[124]
Molecule	CCI	SP	Neurons	Astrocytes	Increased	/	Neurons in the SDH release Substance P, leading to reactive astrogliosis and pain. DHA therapy alleviates pain by reducing the number of reactive astrocytes, and decreasing SP-immunopositive fibers and nNOS-positive neurons.	SDH	Male wistar rats	[21]
Molecule	SNL	TSPO	Astrocytes	Neurons	Increased	p-JNK1-CXCL1-CXCR2 signaling pathway	Early upregulation of spinal astrocyte TSPO alleviates pain by inhibiting the p-JNK1 pathway, thereby reducing astrocytic CXCL1 secretion and attenuating neuronal CXCR2 activation.	SDH	Male SD rats	[125]
Molecule	SNL, CCI	Rbfox1	Neurons	Neurons	Decreased	Alternative RNA splicing pathway	Rbfox1 regulates alternative splicing of NrCAM, affecting neuronal adhesion molecule expression, thereby modulating neuropathic pain	DRG	Male and female C57BL/6 mice	[126]
Molecule	CINP	ADK	Astrocytes	Neurons	Increased	A3AR-IL-10 Signaling	Chemotherapy enhances ADK levels in spinal astrocytes, reducing adenosine signaling at the A3AR subtype, with A3AR agonists alleviating pain by suppressing IL-1β production and increasing IL-10 expression.	Spinal Cord	Male SD rats	[127]

(*Continued*)

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Table 4 (Continued).

Potential Mechanisms	Model	Molecule	Source Cell	Target Cell	Expression	Signaling Pathway	Bio-Function	Tissue	Species	Ref
Molecule	HNP	Wnt5a	Neurons	Astrocytes	Increased	Wnt5a/ROR2/MMP2 Axis	Neuron-secreted Wnt5a signal, via the ROR2 receptor on astrocytes, promoting hyperalgesia and neural circuit polarization in the SDH by regulating IL-1β expression via a Wnt5a-ROR2-MMP2 axis.	SDH	Male C57BL/6 Mice	[128]
Molecule	CCI	SOCS1	Astrocytes	Neuron	Downregulated	/	SOCS1 negatively regulates neuronal sensitization and glial activation, suppressing pain hypersensitivity	SDH	Male Kunming mice	[129]
Molecule	CCI	TMEM34	/	/	Increased	TMEM34/SGK1/FOXO3pathway	The upregulation of TMEM34 in spinal neurons and astrocytes promotes the activation of these cells through the TMEM34/SGK1/FOXO3 signaling axis, thereby causing pain.	Spinal cord	Male SD rats	[130]

Notes: "/" means not mentioned in the article.

Abbreviations: CCI, Chronic constriction injury; SNL, Spinal nerve ligation; NRC, nerve root compression; SCI, chronic constriction injury of the sciatic nerve; SNI, Spared nerve injury; CIPN, Chemotherapy-induced peripheral neuropathy; OIH, Opioid-Induced Hyperalgesia; GLT-1, Glutamate transporter-1; NE, Norepinephrine; Wnt5a, Wingless-Type MMTV Integration Site Family, Member 5A; S1PR1, Sphingosine-1-Phosphate Receptor 1; RGS, Regulator of G-Protein Signaling; GPCR, G-Protein Coupled Receptor; P2X3, P2X Purinoceptor 3; MAPK, Mitogen-Activated Protein Kinase; CXCR, C-X-C Motif Chemokine Receptor; JNK, c-Jun N-terminal Kinase; A3AR, Adenosine A3 Receptor; ROR2, Receptor Tyrosine Kinase-Like Orphan Receptor 2; MMP2, Matrix metalloproteinase-2; TMEM34, Transmembrane Protein 34; SGK1, Serum- and Glucocorticoid-Regulated Kinase 1; FOXO3, Forkhead Box O3; SDH, Spinal dorsal horn; DRG, dorsal root ganglia; SD, Sprague-Dawley.

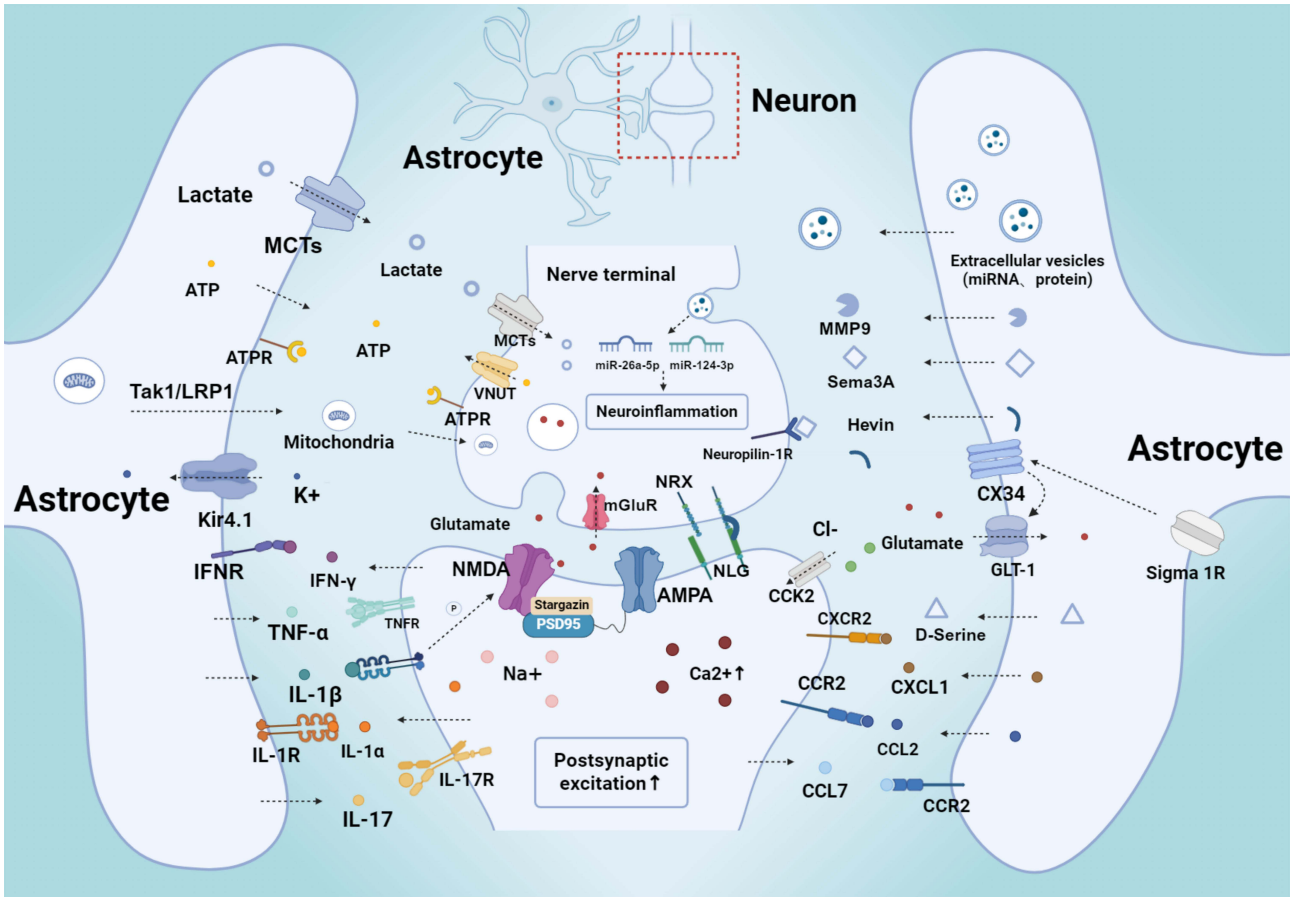

Figure 1 Astrocyte-Neuron Crosstalk Mechanisms and Molecular Mediators in Neuropathic Pain. Activated astrocytes regulate neuronal activity and synaptic plasticity via multiple interconnected mechanisms. These include direct structural modulation of the tripartite synapse, release of proinflammatory cytokines (eg, IL-1β, TNF-α, IL-6, IL-17, IFN-γ, IL-33, CSF-1) and chemokines (eg, CCL2, CXCL1, CXCL13), and secretion of gliotransmitters such as ATP, D-serine, and glutamate. In addition, astrocyte-derived factors, including Hevin and MMPs, orchestrate excitatory synapse formation, while exosomes and metabolic signals further contribute to central sensitization and the maintenance of neuropathic pain. The red box marks the tripartite synapse composed of astrocytes, presynaptic membrane and postsynaptic membrane, with its detailed magnified diagram shown inside the box. Black dashed arrows indicate the transport, paracrine secretion and transcellular signal regulatory pathways of various molecules and extracellular vesicles. The upward solid arrow denotes enhanced postsynaptic excitation.

homeostasis and energy metabolism further potentiate cytokine production and glutamatergic transmission, establishing a feed-forward loop that sustains neuronal hyperexcitability. Despite their molecular diversity, these mechanisms ultimately converge on common downstream events, including enhanced excitatory synaptic plasticity, central sensitization, and persistent neuropathic pain.

Despite significant progress in recent years, several challenges remain. First, most studies have been conducted in rodent models, with limited evidence from human patients. Although rodent models provide important mechanistic insights, species differences may limit the direct translatability of findings. Second, astrocyte functions are highly context- and region-dependent, and may exhibit distinct roles across different brain regions, disease stages, or physiological states.[133,134] Moreover, astrocyte-neuron interactions involve multiple inflammatory mediators, metabolites, neurotrophic factors, and ion channels, which may act synergistically or antagonistically.[9,17,135] Future studies combining single-cell sequencing, multi-omics analyses, and systems biology approaches, along with advanced neuroimaging techniques, are needed to comprehensively map these molecular networks and dynamically monitor astrocyte function in vivo.[136–138] Astrocytes involved in neuropathic pain are increasingly recognized as a heterogeneous population with distinct functional phenotypes. Rather than representing a uniform cell type, astrocytes exhibit marked region-specific and state-dependent characteristics. In particular, homeostatic astrocytes preserve synaptic homeostasis by maintaining glutamate uptake, ion balance, and metabolic support, whereas reactive astrocytes acquire diverse phenotypes that differentially regulate neuroinflammation, synaptic remodeling, and neuronal excitability following nerve injury. Consequently, distinct astrocyte subpopulations are likely to contribute to

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different stages of neuropathic pain, including its initiation, maintenance, and resolution. Future studies integrating single-cell multi-omics and spatial transcriptomics are needed to define the molecular and functional characteristics of these astrocyte subsets and their dynamic interactions with neurons. Such advances will facilitate the development of precision therapies that selectively target pathogenic astrocyte populations while preserving their essential homeostatic functions. In addition, it is also worth noting that the bidirectional communication between microglia and astrocytes represents another critical regulatory axis in neuropathic pain and other CNS disorders.[139,140] Microglia-derived factors such as complement component C1q, TNF-α, and IL-1α can drive the conversion of astrocytes into the neurotoxic A1 phenotype, thereby exacerbating neuronal dysfunction.[141,142] However, this aspect is beyond the scope of the present discussion.

From a translational perspective, while glia-targeted therapeutic strategies have shown promising results in preclinical models, their clinical application remains challenging. Current approaches targeting astrocyte-neuron signaling primarily focus on restoring glutamate homeostasis, inhibiting astrocyte-derived synaptogenic factors, modulating astrocytic inflammatory signaling pathways, regulating connexin-mediated gliotransmission, and interfering with extracellular vesicle-mediated neuron-glia communication. These strategies aim to normalize aberrant synaptic transmission and attenuate central sensitization. A major obstacle is the selective modulation of astrocyte function without inadvertently affecting other glial populations, such as microglia or oligodendrocytes. Enhancing astrocytic glutamate clearance has emerged as a promising strategy for pain modulation. β-lactam antibiotics such as ceftriaxone and cefadroxil reduce extracellular glutamate, suppress neuronal hyperexcitability, and produce significant antinociceptive effects in neuropathic and inflammatory pain models.[143] Similarly, clavulanic acid has been shown to alleviate neuropathic pain through GLT-1 dependent mechanisms.[144] Increased transporter activity also dampens spinal astrocyte activation and synaptic hyperexcitability.[108] However, clinical evidence directly demonstrating therapeutic efficacy remains limited. Furthermore, the intimate association of astrocytes with the blood-brain barrier necessitates that therapeutics are designed to efficiently penetrate this barrier while minimizing systemic side effects.[145,146] With advances in nanomedicine, bioengineered materials, and gene editing technologies, more precise and effective intervention strategies may be developed, offering new therapeutic options for patients with neuropathic pain.[147–149]

While most studies have focused on the pronociceptive functions of reactive astrocytes after nerve injury, recent evidence suggests that homeostatic astrocytes are integral components of spinal non-neuronal pain-gating mechanisms. Activation of low-threshold Aβ afferents recruits spinal astrocytes to suppress nociceptive transmission through endogenous adenosine signaling and long-term depression of neurokinin-1 receptor-positive ($NK1R^+$) projection neurons, thereby contributing to endogenous antinociception.[150] This context-dependent functional transition may provide a more comprehensive framework for understanding astrocyte-neuron interactions in neuropathic pain. Under physiological conditions, astrocytes maintain synaptic homeostasis and limit nociceptive transmission, whereas following nerve injury they undergo reactive remodeling and acquire pronociceptive properties that facilitate central sensitization.

In summary, astrocytes play a critical role in the development and maintenance of neuropathic pain. Through inflammatory mediators, metabolic pathways, and synaptic regulation, they form a complex interactive network with neurons. Although key pathways have been partially elucidated, further investigation is required to understand their dynamic changes and molecular mechanisms under different pathological conditions. Targeting astrocytes may provide a novel strategy for the treatment of neuropathic pain and pave the way for more effective, individualized therapeutic approaches.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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