Review article

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Glial cells as target for antidepressants in neuropathic pain

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Abstract: Several forms of chronic pain do not respond to the conventional analgesics, such as opioids, but can be treated with antidepressants, such as serotonin and noradrenalin reuptake inhibitors (SNRIs). Recent studies indicate that noradrenalin signalling is a key target for SNRI-induced analgesia in neuropathic pain. SNRIs inhibit chronic pain by blocking reuptake of noradrenalin and subsequent activation of adrenergic receptors on neurons in the dorsal horn of the spinal cord. However, in the nervous system, various subtypes of adrenergic receptors are highly expressed by astrocytes and microglial cells. Activation of these receptors on astrocytes engages complex intracellular signalling pathways and prevents inflammatory changes of microglia, which in turn can affect neuronal activity. Hence, SNRIs-induced modulations of the glial cell physiology can impact neural circuit functions and pain perception. In this review, we summarize our current knowledge on the impact of SNRIs on glial cells and in modulating chronic pain in experimental animal models.

Keywords: adrenergic receptors; astrocytes; chronic pain; microglia; serotonin and norepinephrine reuptake inhibitors (SNRI).

Zusammenfassung: Konventionelle Analgetika wie Opioide helfen häufig nicht bei chronischen Schmerzen, interessanterweise im Gegensatz zu Antidepressiva wie Serotonin- und Noradrenalin-Wiederaufnahmehemmern (SNRI). Neuere Untersuchungen zeigen nun, dass in der Tat Noradrenalin-abhängige Signalwege bei SNRI-induzierter Analgesie beteiligt sind. SNRIs induzieren erhöhte Noradrenalin-Spiegel im Dorsalhorn des Rückenmarks. Die folgende Aktivierung adrenerger Rezeptoren der Spinalneurone führt zu einer deutlichen Reduktion der neuropathischen Schmerzen. Im Nervensystem werden jedoch verschiedene Subtypen von adrenergen Rezeptoren in hohem Maße von Astrozyten und Mikrogliazellen exprimiert. Die Aktivierung dieser Rezeptoren auf Astrozyten setzt komplexe intrazelluläre Signalwege in Gang und verhindert entzündliche Veränderungen der Mikroglia, die ihrerseits die neuronale Aktivität beeinflussen können. Daher können SNRI-induzierte Modulationen der Gliazellphysiologie die Funktionen neuronaler Schaltkreise und die Schmerzwahrnehmung beeinflussen. In dieser Übersicht fassen wir unser aktuelles Wissen über die Auswirkungen von SNRIs auf Gliazellen und die Modulation chronischer Schmerzen in experimentellen Tiermodellen zusammen.

Schlüsselwörter: chronischer Schmerz; adrenerge Rezeptoren; Astrozyten; Mikrogliazellen; Noradrenalin; Serotonin- und Noradrenalin-Wiederaufnahmehemmer (SNRI).

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Introduction

Chronic pain is one of the most common global health problems, which incurs high healthcare costs and loss of productivity. In addition to impaired physical well-being, chronic pain has been linked to numerous mental comorbidities such as anxiety and depression (Bair et al., 2003), drug dependence (Salsitz, 2016), and reduced quality of life (Bair et al., 2003; Dueñas et al., 2016). At present most of the analgesic drugs used in the treatment of chronic pain including opioids and antidepressants tend to exhibit tolerance and side effects. Also, a consistent fraction of patients does not respond to commonly used analgesic drugs. For this reason, there is a global effort to find novel targets to develop more effective analgesic drugs with reduced or no side effects.

In general, analgesic drugs seem to mainly target neuronal excitability and synaptic plasticity (Carroll et al., 2007; Nakajima et al., 2012). However, very little is known about the mode of action of most of the analgesics on glial cells – a major class of cells in the nervous system. Several recent studies have demonstrated that two types of glial cells, i.e. astrocytes and microglia, play critical roles in the pathogenesis of chronic pain and its long-term maintenance (Ji et al., 2016). Indeed, activated glial cells release neuroactive factors that can be *pain-inducing* or *pain-alleviating*, which engage neurons in bidirectional communication and lead to short- and long-term changes in the neural circuit of pain. One strategy to relieve short-term pain is to block glial cell activation in response to injury, but a more promising strategy is to prompt glia to release neuroactive molecules that can avert pain induction or even lead to analgesia.

Among antidepressants, SNRIs are most frequently used to treat refractory forms of neuropathic pain (Finnerup et al., 2005, 2015; Lee and Chen, 2010). SNRIs increase the availability of two neuromodulators, serotonin (5-hydroxytryptamine, 5-HT) and noradrenalin (NA), which are known to modulate pain perception. 5-HT and NA can exert a dual effect on pain hypersensitivity (Tavares et al., 2021). 5-HT suppresses pain through the activation of 5-HT1A/B and 5-HT7 receptors in the spinal cord (Newman-Tancredi et al., 2018; Santello et al., 2017), while the activation of 5-HT3 and 5-HT2A receptors facilitates pain (Oyama et al., 1996). Although 5-HT can modulate pain, NA is the primary neuromodulator responsible for the analgesic effects of SNRIs. For NA, two mechanisms of action have been suggested (**1**) activation of noradrenergic descending pathways and (**2**) release of NA from sympathetic fibers sprouting into dorsal root ganglia (DRGs) (Kremer et al., 2016). Similar to 5-HT, while NA can reduce hyperalgesia via activation of α2 and β2 adrenergic receptors (Yalcin et al., 2010), it can evoke hyperalgesia via activation of α1 adrenergic receptor (Kohro et al., 2020). Additionally, pain conditions can induce plastic changes in specific cell-types, which can further contribute toward the pain-relieving effect of antidepressants (Kimura et al., 2013). The pain modulation by adrenergic pathways could be further shaped by immune cells and cytokines. Indeed, activation of α2a adrenergic receptors might contribute to the long-term analgesia by preventing neuroinflammatory changes such as reduced production of inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and prostaglandins (Liu and Eisenach, 2005). Here, we want to highlight that even though we know various sites of action of SNRIs, the precise mechanism of their action on chronic pain remains elusive. It is tempting to speculate that SNRIs engage distinct pathways involving neurons and glial cells, and modulate several regions across the brain, spinal cord and DRGs (Obata, 2017). Since astrocytes and microglia express a wide variety of adrenergic receptors, these drugs could engage astrocytic and microglial signaling mechanisms to influence neuronal activity and synaptic plasticity. In this review, we will highlight some of the known effects of SNRIs on glial cells in pain modulation.

Astrocytes in pain

Astrocytes are one of the most abundant glial cells in the CNS and account for 20–40% of all glial cells (Herculano-Houzel, 2014). Astrocytes perform homeostatic functions, such as maintenance of extracellular ion (K^+) concentrations and neurotransmitter levels (glutamate and GABA), regulation of blood brain barrier, and provide energy substrates (e.g., lactate) to neurons. Several studies suggest that astrocyte activation can induce long-lasting changes in the neural circuit of pain, and play a major role in the amplification, maintenance and chronicity of pain (Ji et al., 2013). Reactive astrocytes release a variety of cytokines and chemokines, such as TNF-α and CCL2, which can potentiate chronic pain by loss of GABAergic inhibition and by strengthening pain memory traces, respectively (Gosselin et al., 2010; Kronschläger et al., 2016; Tang et al., 2021). Furthermore, astrocytes in chronic pain conditions lose their homeostatic properties such as regulation of ion and neurotransmitter levels and their receptor expression, leading to neuronal hyperexcitability and subsequently contribute to pain induction (Li et al., 2019). For example, it

has been shown that in response to peripheral nerve injury (PNI), the primary somatosensory (S1) cortex astrocytes upregulate glutamate receptors such as mGluR5, which mediates aberrant Ca^{2+} signaling and enhanced production of the synaptogenic factor thrombospondin-1 (TSP1). TSP1 promotes maintenance of chronic pain by formation of aberrant synapses that lead to the rewiring of neural circuits of pain (Kim et al., 2016a). Moreover, the optogenetic activation of spinal cord (SC) astrocytes induced mechanical allodynia and thermal hyperalgesia by disinhibiting neurons in the spinal cord dorsal horn (SDH) (Nam et al., 2016; Yamashita et al., 2014). At the same time, inhibiting astrocytic activity can reduce neuropathic pain (Meller et al., 1994).

Astrocytes and their interactions with SNRIs

Astrocytes are known to express several sub-types of α and β adrenergic receptors (Gaidin et al., 2020; Hertz et al., 2010; Salm and McCarthy, 1992), and activation of these receptors can modulate pain. A recent study identified a subgroup of astrocyte that get activated in response to a painful stimulus (intraplantar capsaicin injection). These astrocytes are located in the superficial laminae of the SDH and express transcription factor called Hes5. A direct chemogenetic activation or an activation of α1a receptors on Hes5+ astrocytes induced mechanical hyperalgesia (Kohro et al., 2020). In a PNI model, the specific deletion of α1a in Hes5+ astrocytes enhanced the analgesic action of duloxetine, a drug often prescribed for peripheral diabetic neuropathic pain (DPN) and fibromyalgia patients (Bravo et al., 2019). This finding suggests α1a adrenergic receptors on astrocytes can be a target for co-adjuvant drugs to associate with duloxetine, in order to obtain the same analgesic effect but with a lower doses and side effects (Kohro et al., 2020).

A metabolic profiling study revealed that venlafaxine affects amino acid metabolism, cellular growth, and proliferation pathways in astrocytes (Sun et al., 2017). The analgesic effect of venlafaxine was induced by alteration in the amino acid metabolism and decreased glutamate levels, which in turn impaired glutamate-dependent synaptic plasticity. In addition, venlafaxine inhibited the production of pro-inflammatory cytokines IL-6 and IL-1β, and reduced activation of two important molecular pathways of pain development, STAT3 and JNK (He et al., 2021). Another study showed that a NA and specific serotonergic antidepressant (NaSSA) mirtazapine induce the production of glial cell line-derived neurotrophic factor (GDNF) in astrocytes (Hisaoka-Nakashima et al., 2019), which reduce ectopic discharges within sensory neurons and reversed sensory hypersensitivity developed in neuropathic pain (Boucher et al., 2000).

In conclusion, astrocytes seem to play a key role in pathogenesis of neuropathic pain and might be a target of action of SNRIs (Figure 1 B, C). In future, detailed studies are essential to unravel the mechanism of action of SNRIs on astrocytes and to develop new molecules which further enhance the efficacy of SNRIs in pain treatment.

Microglia in pain

In the CNS, microglia are the resident immune cells and continuously survey the neuropil to clear up cellular debris and infectious agents (Hanisch and Kettenmann, 2007). Microglia have been shown to be active players in the pathogenesis of chronic pain (Ji and Suter, 2007). Pain differs from other neurological diseases for its rapid onset: following treatment with microglial activators and inhibitors, pain behavior will change within minutes to tens of minutes (Berta et al., 2014; Tsuda et al., 2003). Recent studies indicate that neuromodulators released by microglia can rapidly alter synaptic plasticity, a driving force for the pathogenesis of pain after tissue and nerve injury (Luo et al., 2014; Woolf and Salter, 2000).

After PNI, SDH microglia are strongly activated (Guan et al., 2016; Tsuda et al., 2005). This activation requires neuronal activity (Wen et al., 2007; Xie et al., 2009) and the release of sensory neuron-derived pro-inflammatory factors, including colony-stimulating factor 1 (CSF1), caspase-6, neuregulin-1, cytokines such as IL-1β, CCL2, CXCL1, CCL21, extracellular proteases and ATP (reviewed in Inoue and Tsuda, 2018). All these molecules have been shown to efficiently activate distinct receptors on microglia and concomitantly enhance the expression of receptors for these factors, such as P2X4, P2Y12, and CX3CR1. The activated microglia further increase production of TNF-α, IL-1β and brain-derived neurotrophic factor (BDNF), which in turn fine-tunes excitatory and inhibitory synapses, and ultimately enhance pain signal transmission to the brain. For example, TNF-α and IL-1β enhance excitatory and suppress inhibitory synaptic transmission, while BDNF disinhibits GABA-mediated inhibition in the SC (Guan et al., 2016; Kawasaki et al., 2008). Since microglial cells are engaged in neuroinflammation after nerve injury and influence synaptic connectivity and neurotransmission, they are critical for the induction of hyperalgesia and allodynia in chronic pain conditions (Figure 1 B, C).

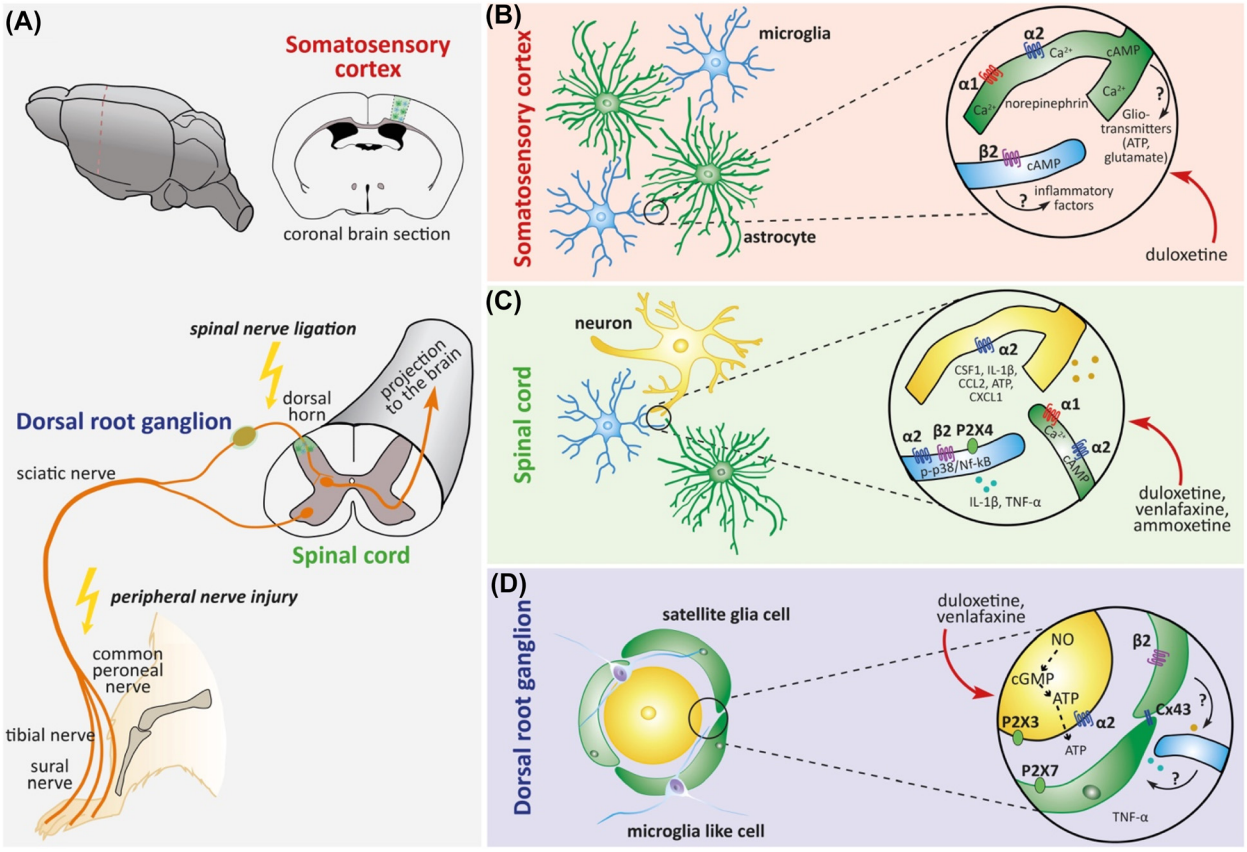

Figure 1: Action of SNRIs in peripheral and central nervous system glial cells and their involvement in chronic pain.
(A) SNRIs induce analgesia by acting in areas from the central and peripheral nervous system. **(B)** In the brain, the increase in noradrenalin concentration in the synaptic cleft induced by SNRIs can activate α1 and α2 receptors in astrocytes (green), and β2 receptors in microglia (blue). The activation of α1 adrenergic signaling in somatosensory cortex astrocytes triggers rapid astrocytic Ca^{2+} elevation (Agarwal et al., 2017), while activation of α2 receptors leads to a simultaneous increase in intracellular Ca^{2+} and reduced cAMP levels, but their consequences to the analgesic effect of SNRI is least understood. β2 receptors activation in microglia elevates intracellular levels of cAMP, which in turn can modulate neuroinflammation and impair cortical experience-dependent plasticity. The potential anti-inflammatory effect of β2 receptor activation in cortical microglia for the analgesic effect of SNRIs remains unexplored. **(C)** The action of noradrenalin in the spinal cord neural circuit seems to be a key mechanism responsible for the analgesic effect of SNRIs. Noradrenalin inhibits projections and interneurons (yellow) in the dorsal horn through activation of α2 adrenergic receptors. However, adrenergic receptors in both microglia (blue) and astrocytes (green) in the spinal cord can influence the analgesic effect of SNRIs. Activation of the α1 receptor in astrocytes of the dorsal horn induces pain, but consequences of α2 activation remains unexplored. α2 and β2 adrenergic receptors activation in spinal microglia reduces the activation p38/NF-κB pathway and the release of pro-inflammatory and neuroregulatory mediators during neuropathic pain. **(D)** The analgesic effect of SNRIs in the peripheral nervous system occurs by the activation of the β2 receptor in SGCs (green). This activation suppresses the release of ATP and TNF-α, and reduces microglia-like cells/macrophages (blue) activation in DRGs. ATP can induce mechanical sensitization by acting in P2X3 directly in nociceptors (yellow) or inducing the expression of TNF by acting in P2X7 receptors in SGSc. Given that TNF disrupts gap junctions, the SNRIs may play an indirect effect on connexins, such as connexin-4. Ca^{2+} = calcium ions; cAMP = cyclic adenosine monophosphate; ATP = adenosine triphosphate; CSF1 = colony-stimulating factor 1; IL-1β = interleukin 1 beta; TNF-α = tumor necrosis factor alpha; cGMP = cyclic guanosine monophosphate; Cx43 = connexin 43.

Microglia and their interactions with SNRIs

In particular, microglial cells express α2 and β2 adrenergic receptors, which are well known for their role in neuropathic pain (Kremer et al., 2016). Activation of these receptors was shown to attenuate microglial reactivity through reduced activation p38 MAPK pathway (Morioka et al., 2009; Zhang et al., 2016b) and can ameliorate neuropathic mechanical hypersensitivity (Choucair-Jaafar et al., 2009). In models of neuropathic pain, such as DNP or vincristine-induced neuropathic pain, duloxetine treatment reduced microglial activation (Tawfik et al., 2018). Moreover, duloxetine downregulated TNF-α and NGF levels in a rat model of intervertebral disk (IVD) degeneration (Handa et al., 2016).

Interestingly, intrathecal injection of Poly Lactic-*co*-Glycolic Acid (PLGA) nanoparticles containing a low dose of duloxetine was able to attenuate the p38/NF-κB pathway and the production of inflammatory cytokines in the rat spinal nerve ligation (SNL) model (Kim et al., 2021). Several studies highlighted an inhibitory effect of duloxetine on microglia P2X4R (Nagata et al., 2009; Yamashita et al., 2016), and the consequent analgesic effects persisted even after 5-HT and/or NA signals were inhibited by 5-HT depletion or a NA neurotoxin in a PNI induced pain hypersensitivity (Yamashita et al., 2016). Duloxetine results in a general inhibition of microglia in the spinal cord that associates with the reduction of pain hyperalgesia. In astroglia–microglia co-culture, venlafaxine prevented microglial activation, reduced pro-inflammatory cytokine secretion (IL-6 and INF-γ), and increased TGF-β release (Vollmar et al., 2008).

A potent SNRI ammoxetine was found to have analgesic effect on neuropathic pain, fibromyalgia-related pain or inflammatory pain models (Zhang et al., 2016, 2018). In a rat DNP model, which shows increased activation of microglia but not astrocytes in the SC, four weeks of ammoxetine treatment significantly reduced mechanical allodynia and improved depressive-like behavior. Similar to other SNRIs, ammoxetine reduces microglial activation, accumulation of pro-inflammatory cytokines and activation of p38 and c-Jun N-terminal kinase (JNK) in the SC (Zhang et al., 2018).

Taken together, a general mode of action of SNRIs on microglial cells is to prevent their activation and subsequent production of inflammatory cytokines, which contributes to the overall analgesic efficacy of these class of drugs (Table 1). Understanding the impact of microglia in analgesic efficacy of SNRIs can promote the development of new specific drugs that have little to no severe complications or better fit for other neuropathic conditions.

Peripheral glia in pain

For a holistic targeting of chronic pain, it is of utmost importance to not only to comprehend the changes in the SC and brain, but also the cellular and molecular changes in the DRGs (Berger et al., 2021; Berta et al., 2017; Esposito et al., 2019; Liem et al., 2016). DRGs are the part of the peripheral nervous system (PNS) recognized as targets for (neuro)-modulation to combat chronic pain (Berta et al., 2017). In the DRG, two types of glia namely satellite glial cells (SGCs) and macrophages as microglia-like cells (MLCs) are central to pain cascades (Ahimsadasan et al., 2022; Murray et al., 2021). SGCs closely attach to neurons and share many properties with astrocytes of the CNS (Hanani, 2005), including recycling the excess of extracellular glutamate (Carozzi et al., 2008), potassium buffering (Tang et al., 2010) and gap junctions (connexin 43) coupling (Spray and Hanani, 2019). SGCs become gap-junction coupled to neurons in response to neuronal injury (Kim et al., 2016b; Spray and Hanani, 2019). The macrophages in the DRGs are equivalent to the microglia of the CNS (Mori et al., 2003) and perform the task of an immune system, and get activated during acute and chronic pain (Yu et al., 2020).

When considering the sensory processing along the DRGs, Schwann cells are important cellular partners. They are the myelinating cells of the PNS and are in close contact with the neurons and immune cells. Upon peripheral injuries, Schwann cells are involved in the enhanced release of chemokines/cytokines (MCP-1, TNFα, etc.), recruitment of macrophages, gene expression changes in the sensory neurons (Martini et al., 2008; Ohtori et al., 2004; Poplawski et al., 2018; Wagner and Myers, 1996).

Interestingly, direct stimulation of DRG neurons releases ATP, activates surrounding SGCs via P2X7 receptors and leads to an increased TNF-α release from SGCs. This

Table 1: Clinically used antidepressants and their targets in CNS and PNS glial cells.

SNRI	Target	Cell type	CNS/PNS region	References
Duloxetine	GFAP, connexin 43, p38/NF-κB TNF-α, Iba1	Astrocytes, microglia SGCs,	SC, DRG	Tawfik et al. (2018), Jeanson et al. (2016), Okada et al. (2020), Sun et al. (2012), Handa et al. (2016), and Kim et al. (2021)
Ammoxetine	p-p38, p-JNK	Microglia	SC	Zhang et al. (2018)
Venlafaxine	S100B, β2-AR, iba1	Astrocytes, SGCs, microglia	PNS (DRG)	Zychowska et al. (2015) and Bohren et al. (2013)

communication between neurons and glial cells could be disrupted by blocking L-type calcium channel (Zhang et al., 2007). Furthermore, the activation of P2X7 receptors in SGCs reduced pain by downregulating P2X3 receptors in nociceptive neurons (Chen et al., 2008).

DRG glial cells and their interactions with SNRIs

Still, there is a no clear description of the exact mechanisms of action of SNRIs on the glial cells of the DRGs. Recent studies showed the involvement of various chemokines and cytokines in the induction and chronification of pain (Gosselin et al., 2010; Tang et al., 2010). Several SNRIs such as venlafaxine, duloxetine, and terbutaline have been shown to decreased TNF-α level in SGCs and attenuated neuropathic allodynia through a mechanism dependent on β2-AR (Bohren et al., 2013; Handa et al., 2016), which is exclusively expressed on SGCs, and not on neurons (Shen et al., 2022). In addition, venlafaxine was able to induce analgesic effects and weaker allodynia by reducing microglia activation as detected by Iba1-immunolabeling in the DRG (Zychowska et al., 2015).

Although the mode of action of SNRIs in DRGs is unclear, they may attenuate sensitivity to pain by reducing the recruitment of immune cells to the DRGs through inhibition of ATP and TNF-α release, which leads to decreased interaction between SGCs and DRG neurons (Figure 1D). However, an extended analysis of the signaling pathways affected by SNRIs in DRGs is needed to capture the full extent of action of these drugs across the nervous system.

Perspective

It is evident that we know very little about the role of glial cells across the nervous system in the pain modulation. In the context of the pain pathophysiology, glial cells have been mostly studied in the context of neuroinflammation with a limited number of cellular markers and the handful of chemokines and cytokines. Another caveat has been that most of the studies outlining the role of glia cells in pain have been performed in the cell culture system, which many times couldn't be directly interpolated *in vivo*. With emerging imaging technologies, cell-type specific expression of genetically encoded ion sensors, optogenetics and chemogenetics tools, mouse transgenic tools, and high-throughput single cell RNA-sequencing, metabolomics and proteomics, will enable glial-biologists and pain researchers to work closely to dissect the role of astrocytes and microglial cells in pain modulations and chronification in the PNS and CNS.

The increased understanding of the role glial cells in chronic pain will not only help us tackle already know pain conditions, but also to develop an efficient treatment strategy for the newly arising conditions. For examples, COVID-19 often causes peripheral or central neuroinflammation, it is anticipated that several chronic pain complications of COVID-19 will be neuropathic (Drożdżal et al., 2020). Although antidepressants such as SNRIs are effective in the treatment of a small class of neuropathic pain conditions, it might be worth repurposing SNRIs to treat COVID-19 related neuropathic pain. In the long-term, the key aim is to gain a precise understanding of the analgesic mechanisms of antidepressants, and to identify distinct cellular targets of these drugs. These developments will enable to further develop specific drugs or therapies to treat neuropathic pain without undesirable cognitive side effects of SNRIs.

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