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Sigma-1 receptor: A drug target for the modulation of neuroimmune and neuroglial interactions during chronic pain

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ABSTRACT

Immune and glial cells play a pivotal role in chronic pain. Therefore, it is possible that the pharmacological modulation of neurotransmission from an exclusively neuronal perspective may not be enough for adequate pain management, and the modulation of complex interactions between neurons and other cell types might be needed for successful pain relief. In this article, we review the current scientific evidence for the modulatory effects of sigma-1 receptors on communication between the immune and nervous systems during inflammation, as well as the influence of this receptor on peripheral and central neuroinflammation. Several experimental models of pathological pain are considered, including peripheral and central neuropathic pain, osteoarthritic, and cancer pain. Sigma-1 receptor inhibition prevents peripheral (macrophage infiltration into the dorsal root ganglion) and central (activation of microglia and astrocytes) neuroinflammation in several pain models, and enhances immune-driven peripheral opioid analgesia during painful inflammation, maximizing the analgesic potential of peripheral immune cells. Therefore, sigma-1 antagonists may constitute a new class of analgesics with an unprecedented mechanism of action and potential utility in several painful disorders.

1. Introduction: sigma-1 receptors as a one-of-a-kind type of drug target and the need for novel analgesics

The sigma-1 receptor is a Ca^{2+}-sensing chaperone [1]. Currently, to the best of our knowledge there is no drug on the market, for any therapeutic indication, that directly modulates a chaperone activity. Therefore, sigma-1 receptors are not only a novel but also a one-of-a-kind type of drug target. This peculiarity of sigma-1 receptors has attracted considerable attention from pharmacologists around the world during recent decades.

At the subcellular level, sigma-1 receptors are particularly enriched in the endoplasmic reticulum membranes associated with mitochondria [1]. In situations of cellular stress, when intracellular Ca^{2+} increases, sigma-1 receptors are activated and translocated to other areas of the cell, particularly to areas close to the plasma membrane, where they physically interact with several membrane proteins [2,3]. These protein partners of sigma-1 receptors include several ion channels, such as glutamate receptors of the NMDA (*N*-methyl-*D*-aspartate) subtype, and G-protein-coupled receptors, such as opioid receptors. The sigma-1 receptor interactome includes many more protein targets than those mentioned above, as described in a recent review [3,4]. Once sigma-1 receptors interact with their proteins partners, they act as a regulatory subunit and have a profound impact on neurotransmission [2,3]. Taking into account the mechanism of action of these pharmacological receptors, it is not surprising that sigma-1 ligands have been proposed as therapeutic tools for the treatment of several pathologies affecting the nervous system, including depression and anxiety [5], memory and learning disorders [6], and pain [3,7]. This review article focuses on a

Abbreviations: ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CX3CL1, C-X3-C Motif Chemokine Ligand 1; CCL-2, C-C Motif Chemokine Ligand 2; Cx43, connexin 43; DRG, dorsal root ganglia; GDNF, glial-derived neurotrophic factor; IL, interleukin; MCP1, monocyte chemoattractant protein-1; MRI, magnetic resonance imaging; NGF, nerve growth factor; NMDA, *N*-methyl-*D*-aspartate; PET, positron emission tomography; TNF, tumor necrosis factor.

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Table 1
Summary of studies that describe the cellular location of sigma-1 receptors and their role in neuroimmune interactions and neuroinflammation in different pain models. The table does not show studies focused on the distribution of sigma-1 receptors in the absence of any disease state.

Type of pain	Pain model	Species	Sex	Tissue	Sigma-1 receptor expression	Sigma-1 ligand/KO	Route	Effect on neuroimmune interaction or neuroinflammation	Effect on pain	References
Inflammatory pain	Carrageenan i.pl.	Mouse	Female	Hindpaw	–	BD1063/ S1RA*	s.c. and i.pl.	↑ effect of endogenous opioid peptides from immune cells	↓ mechanical and heat hyperalgesia	[37]
		Rat	Male	Spinal cord	–	BD-1047	i.t.	↓ D-serine and serine racemase in astrocytes	–	[73]
	Zymosan i.pl.	Rat	Male	Spinal cord	Neurons	BD-1047	p.o.	↓ microgliosis ↓ IL-1β	–	[67]
		Rat	Male	Sciatic nerve	Schwann cells	FTC-146*	Injection at the neuroma site	–	↓ mechanical allodynia	[45]
		Mouse	Female	Dorsal root ganglion	Neurons	KO	–	↓macrophage infiltration ↓ CCL-2 and IL-6	↓ cold and mechanical allodynia	[53,58]
	Spared nerve injury	Mouse	Male & female	–	–	S1RA*	s.c.	↑ effect of endogenous opioid peptides from unknown sources	↓ mechanical and heat hypersensitivity	[58]
Peripheral neuropathic pain		Rat	Male	Dorsal root ganglion	Neurons	Inhibition of expression by viral vector	Microinjection into the dorsal root ganglion	–	↓ mechanical, heat and cold hypersensitivity	[57]
	Spinal nerve ligation	Rat	Male	Dorsal root ganglion	Neurons	–	–	–	–	[54]
	Chronic constriction injury	Mouse	Male	Spinal cord	Astrocytes	BD-1047	i.t.	↓ astrocytosis	↓ mechanical allodynia	[68]
					Astrocytes	BD-1047	i.t.	↓ D-serine in astrocytes	↓ mechanical allodynia	[74]
					–	BD-1047	i.t.	Effects opposite to astrocyte activation	↓ mechanical allodynia	[75]
Central neuropathic pain	Spinal cord contusion	Mouse	Female	Spinal cord	–	KO		↓ TNF and IL-1β	↓ mechanical and heat hypersensitivity	[71]
					–	S1RA	i.p.	↓ TNF and IL-1β	↓ mechanical and heat hypersensitivity	[72]
	Spinal cord hemisection	Mouse	Male	Spinal cord	Astrocytes	BD-1047	i.t.	↓ astrocytosis ↓ Cx43	↓ mechanical allodynia	[69]
				Dorsal root ganglion	–	S1RA	i.p.	↓ BDNF	↓ mechanical allodynia	[59]
Osteoarthritis	Intra-articular monoiodoacetate	Mouse	Male	Spinal cord	–	S1RA	i.p.	↓ microgliosis ↓ TNF and IL-1β	↓ mechanical allodynia	[59]
				Medial prefrontal cortex	–	S1RA	i.p.	↓ microgliosis	↓ mechanical allodynia ↓ cognitive deficits ↓ depressive-like behaviors	[78]
Cancer pain	Injection of cancer cells into the tibia	Rat	Female	Spinal cord	–	BD-1047	i.t.	↓ microgliosis ↓TNF	↓ mechanical allodynia	[70]
Pain induced by chemical algogens	Formalin i.pl.	Mouse	Male	Spinal cord	Astrocytes	BD-1047	i.t.	↓ activation of astrocytic aromatase	↓ nociceptive responses	[64]
	NMDA i.t.	Mouse	Male	Spinal cord	–	PRE-084	i.t.	↑ astrocyte activation	↑ nociceptive responses	[75]

BDNF: brain-derived neurotrophic factor, IL: interleukin, i.pl.: intraplantar, i.t.: intrathecal, i.p.: intraperitoneal, KO: knockout, NMDA: *N*-methyl-*D*-aspartic acid, p.o.: oral administration, s.c.: subcutaneous, TNF: tumor necrosis factor.
* Indicates that acute drug treatments were performed when pain behavior was fully developed.

detailed examination of specific aspects of the role of sigma-1 receptors in pathological pain.

Approximately 20 % of individuals in developed countries suffer from chronic pain [8], and this proportion rises to 30 % when only the adult population is considered [9]. Therefore, it is not an exaggeration to say that millions of people suffer from chronic pain, making this issue a major public health concern [10,11]. Conventional analgesics such as opioids, nonsteroidal anti-inflammatory drugs, and gabapentinoids show limited analgesic efficacy in many chronic pain conditions, or significant side effects that strongly limit their use [12–14]. The

development of analgesics to modulate new pharmacological targets, and therefore with truly novel mechanisms of action, is rare [15,16], and among the few exceptions is the selective sigma-1 antagonist S1RA (also referred to as MR309 or E-52,862). This new molecular entity is a first-in-class compound that has already shown encouraging results in preclinical studies of relevant pain models and promising results in clinical trials, as described below.

Recent years have seen intense preclinical research on the mechanisms of chronic pain. The importance of the interactions between sensory neurons and non-neuronal cells in the production and maintenance of pain has been firmly established, in particular regarding the role of the immune cells that accumulate in an inflamed area after injury, as well as the neuroinflammatory processes that occur both in the peripheral and central nervous system in several chronic pain pathologies [17,18]. It is thus possible that to optimize pharmacological approaches to pain treatment, it will be necessary to modulate not only the neurotransmission processes from an exclusively neuronal perspective, but also the complex interactions between neurons and other cell types. As described here, the sigma-1 receptor plays an important role in these processes. Our aims here are to review the generalities of the chemical communication between non-neuronal cells and neurons in the generation of chronic pain, and to summarize the scientific evidence that links the actions of sigma-1 receptors with these processes.

2. Neuroimmune interactions in an injured peripheral tissue: the sigma-1 receptor modulates immune-driven opioid analgesia

Neuroimmune interactions in an injured (inflamed) tissue play a vital role in the induction and maintenance of pain. Recruitment of immune cells to the target tissue occurs shortly after peripheral tissue damage. The predominant immune cells at the inflamed site change over time in a coordinated fashion. In general terms, neutrophils are the predominant immune cells during acute inflammation, macrophages play a more relevant role in later stages, and lymphocytes increase their numbers and functions during chronification of the inflammatory process (without, however, diminishing the relevance of the actions of other immune cells as noted above) [19–21]. All of these immune cells produce a wide variety of pro-inflammatory cytokines including tumor necrosis factor (TNF), IL-1β, IL-6, IL17A, as well as lipid mediators including arachidonic acid derivatives such as prostaglandin E2, 5, 6-epoxyeicosatrienoic and 5-hydroxyeicosatetraenoic acid [17,22]. Several of these cytokines are produced only by specific immune cell types (see [22] for more details). The release of these substances (along with others) plays a key role in coordinating the inflammatory response as a whole, not only in terms of the actions of immune cells, but also in terms of vascular and other processes [23–26]. In addition, immune cells, particularly macrophages, also release nerve growth factor (NGF), whose actions are important to restore the density of nerve endings in the injured area [27,28]. The peripheral terminals of nociceptive neurons express receptors not only for NGF, but also for the cytokines and lipid mediators mentioned above. In response to these factors released by immune cells, nociceptors become sensitized, responding with greater intensity to sensory stimuli and promoting pain [4,17,22]. Therefore, sensory neurons act as sensors for chemicals of immune origin, and consequently as sensors for the presence of immune cells in the injured area.

It is important to note that neutrophils, macrophages or lymphocytes are known to produce endogenous opioid peptides such as β-endorphin, enkephalins, dynorphins or endomorphins, which bind to the μ, κ and δ opioid receptors with different preferences [4]. In fact, immune cells are the main source of endogenous opioids during inflammation [29,30]. However, the production of these analgesic molecules is not able to counteract the effects of the multitude of pro-algesic factors that are released during inflammation. As early as the 1 st century BC, Celsus had described pain as one of the cardinal signs of inflammation. As is well known, pain usually tends to subside with the resolution of inflammation and the consequent cessation of immune response in the affected tissue, which highlights the importance of the immune system in neuronal sensitization at the inflamed site.

Sigma-1 receptors, as noted in the previous section, are able to bind opioid receptors acting as a regulatory subunit. The earliest evidence for the modulation of opioid effects by sigma-1 receptors is from 1993, when Chien and Pasternak showed that haloperidol, a dopamine antagonist used clinically as an antipsychotic but which also has high affinity for sigma-1 receptors [31], was able to greatly increase the antinociceptive effects of the μ opioid agonist morphine [32]. Later studies showed that not only haloperidol, but also more selective sigma-1 antagonists such as BD-1063 or S1RA, were able to increase opioid analgesia induced by morphine and other μ-opioids in clinical use, such as oxycodone or fentanyl. Sigma-1 antagonism was also shown to enhance the antinociceptive effect induced by κ agonists such as U50, 488H or naloxone benzoylhydrazone, as well as the effect induced by the δ agonist [D-Pen2, D-Pen5] enkephalin. The multiple drug combinations of sigma-1 antagonists and opioid agonists used in these studies were reviewed previously [3]. Therefore, the effect initially described for the combination of haloperidol and morphine can be considered extensive to other more selective sigma-1 antagonists, as well as to other opioid drugs with different selectivity for the three main opioid receptor subtypes.

We proposed that sigma-1 antagonism could also potentiate opioid analgesia induced by endogenous opioid peptides, and not only that produced by opioid drugs. Sigma-1 antagonism produces antihyperalgesic effects during inflammation both in the rat [33,34] and in the mouse [35,36]. In a recent study we showed that when inflammatory hypersensitivity was fully established in mice, pharmacological blockade of sigma-1 receptors by BD-1063 or S1RA produced a peripherally-mediated opioid antihyperalgesic effect (reversible by the peripheral opioid antagonist naloxone methiodide) in the inflamed paw, without inducing analgesia in other areas without inflammation. This antihyperalgesic effect was dependent on the presence of immune cells (macrophages or neutrophils) in the inflamed site [37], which (as noted above) are the main source of endogenous opioid peptides during inflammation. Therefore, the pharmacological blockade of sigma-1 receptors induces opioid analgesia selectively in the painful area, maximizing the analgesic potential of immune cells that naturally accumulate in the inflamed site. These results are summarized in Table 1. It is important to note that even though sigma-1 antagonism induces (indirect) opioid effects, this does not mean that its effects are completely equivalent to the administration of an opioid drug. In fact, sigma-1 antagonism lacks the limiting side effects that characterize opioid drugs, such as constipation, and also lacks the reinforcing properties of opioids, at least in rodents [38–40]. The latter characteristic is particularly relevant in light of the opioid epidemic currently causing great concern in some parts of the world, particularly in the USA [41].

3. The role of sigma-1 receptors in peripheral neuroinflammation

Schwann cells are the most abundant glial cells in the peripheral nervous system. When a nerve is injured, Schwann cells acquire a repairing phenotype, gaining proliferation capacity and releasing several factors that stimulate the injured axons. These factors include neurotrophins such as GDNF (glial-derived neurotrophic factor), BDNF (brain-derived neurotrophic factor) and NGF, which promote growth and regeneration in the damaged axons, although they also sensitize sensory neurons and therefore promote the development of neuropathic pain [42,43]. These neurotrophins are not the only pronociceptive factors produced by repair Schwann cells: these cells are also able to release ATP, which interacts with purinergic receptors in sensory axons to induce neuronal depolarization [43]. Eventually, Schwann cells produce several pro-inflammatory cytokines (including TNF, IL-6 and IL-1) after nerve damage, which (as discussed in the previous section) contribute to

the sensitization of peripheral sensory neurons and to the recruitment of immune cells. The macrophages, T-cells and mast cells recruited through this mechanism consequently increase the levels of pro-inflammatory cytokines to reinforce sensitization in the nociceptive axons [42,43]. Thus the action of Schwann cells plays a highly relevant role in the generation of neuropathic pain.

In intact nerves, Schwann cells strongly express sigma-1 receptors [44,45], and their expression is maintained when the nerve is damaged and Schwann cells proliferate [45]. The number of these cells increases after partial section of the sciatic nerve in rats, resulting in a local increase in the density of sigma-1 receptors at the neuroma. These reactions made it possible for the sigma-1 radioligand [18 F]FTC-146 to detect the site of peripheral nerve damage when it was used as a probe in positron emission tomography and magnetic resonance imaging (PET/MRI) studies [45]. Sigma-1 receptors at the site of nerve damage may play an important functional role, since the administration of FTC-146 at the neuroma site was shown to reduce sensory hypersensitivity [45]. However, more studies are needed to clarify whether the action of this sigma-1 ligand in neuropathic pain occurs at the Schwann cell level or at the neuronal level. It would also be interesting to determine whether the administration of sigma-1 ligands is able to alter the proliferation of Schwann cells or the immune cells that are recruited to the injured site, or to alter the levels of pronociceptive factors at the site of nerve damage.

During chronic pain, peripheral neuroinflammation also occurs at the level of the dorsal root ganglia (DRG), where the bodies of the peripheral sensory neurons are located. Most studies on this process have focused on the effects seen after peripheral nerve injury. Satellite cells, which surround the bodies of peripheral sensory neurons, are among the first glial cells to be activated after nerve injury. One of the factors that produces the activation of satellite cells is ATP released from the neuronal soma by the nociceptive activity induced by nerve injury [46]. After nerve damage, mainly neurons but also active satellite cells produce BDNF, which contributes to both axonal regeneration and nociceptive sensitization [47,48]. Active satellite cells produce TNF, which, in turn, participates in the increased excitability of sensory neurons [46]. In addition to the production of TNF, active satellite cells release specific proteases that cleave the chemokine fractalkine (also known as CX3CL1) from the plasma membrane of the bodies of sensory neurons, converting it to its active soluble form [49]. Fractalkine is one of the most important signals for macrophage invasion of the DRG, along with chemokine CCL-2 (also called MCP1, for monocyte chemoattractant protein-1), which is released by damaged neurons [42]. Macrophages are arrayed in a characteristic distribution in the DRG, surrounding the bodies of damaged neurons, and therefore establishing very close contact with them [50]. Macrophages release pro-inflammatory cytokines such as IL-6 (among others), which sensitize the sensory neurons with which they make contact as well as neighboring neurons. These neighboring cells, despite not being damaged by nerve injury, are sensitized by the local pro-inflammatory environment of the DRG [42]. T-cells, attracted by macrophages to DRG [51], also contribute to DRG neuroinflammation, and are of great importance in neuropathic pain development [52]. In contrast, neutrophils do not appear to be recruited to the DRG after nerve injury [53], except when inflammation in the nerve is particularly prominent after injury [42].

The role of sigma-1 receptors in the DRG during neuropathic pain has been explored in recent studies. The DRG contains a much higher density of sigma-1 receptors than several central areas important in pain processing, such as the dorsal spinal cord, basolateral amygdala, periaqueductal gray, and rostroventral medulla [39]. Although the first study to describe the location of sigma-1 receptors in the rat DRG reported their presence in both neurons and satellite cells [54], later studies in mice and rats showed that sigma-1 receptors exhibited a specific neuronal distribution [53,55–57]. After damage to the peripheral nerve, sigma-1 receptors of the neuronal soma from damaged neurons are activated (purportedly due to the increase in intracellular Ca^{2+} induced by the injury) and translocate from intracellular locations to areas close to the plasma membrane [53,57]. It is interesting to note that injured neurons with translocated sigma-1 receptors are mainly the same cells that show concentrated macrophages surrounding the neuronal body. It is thus possible that sigma-1 receptors play a relevant role in neuron–macrophage communication in this context [53]. In this connection, sigma-1 receptor knockout mice showed a marked decrease in CCL-2 production at the DRG, with a consequent reduction in macrophage infiltration in this peripheral nervous tissue [53]. The decrease in macrophages in these mutant sigma-1 knockout mice was accompanied by a decrease in IL-6 content in the injured DRG [53], and therefore resulted in a less pro-inflammatory environment. Sigma-1 knockout mice show decreased neuropathic sensory hypersensitivity [53,58], as did wild-type rats in which viral vectors administered into DRG at the time of nerve injury were used to induce a sustained decrease in sigma-1 receptor expression in peripheral sensory neurons [57]. It is likely that (as seen in sigma-1 knockout mice) pain amelioration was supported by the prevention of peripheral neuroinflammation in wild-type animals treated with viral vectors.

A further finding relevant to peripheral neuroinflammation is that chronic systemic treatment with S1RA, before neuroinflammation was fully established, reduced the increase in BDNF levels in the DRG during the development of experimental osteoarthritis in the knee [59]. Although BDNF in the DRG is produced by both sensory neurons and satellite cells [48], taking into account that sigma-1 receptors are apparently not present in the latter, it is likely that the decrease in the levels of this neurotrophin in response to S1RA treatment is due to direct sigma-1 receptor inhibition on peripheral neurons. However, given the intense communication between neurons and satellite cells, it cannot be ruled out that the decrease in neuronal activity induced by S1RA indirectly affects the activation of satellite cells and hence the levels of BDNF produced by these glial cells. More studies are needed to clarify this particular aspect of the effect of sigma-1 receptors on the peripheral neuroinflammatory responses.

Studies that explored the role of sigma-1 receptors in peripheral neuroinflammation are summarized in Table 1.

In summary, although additional studies are still needed to fully understand the influence of sigma-1 receptors in the activity of different types of glial and immune cells during peripheral neuroinflammation induced by chronic pain, the scientific evidence to date indicates that these receptors play a relevant role in this process.

4. Role of sigma-1 receptors in central neuroinflammation

There are two glial cell types whose role is decisive in the events that take place in the spinal cord dorsal horn during chronic pain: microglia and astrocytes. Microglia are immune cells of the central nervous system equivalent to peripheral macrophages. CCL-2 and ATP produced by the central terminals of peripheral sensory neurons play a key role in microglial activation [42,46]. In addition, active microglia are able to cleave fractalkine from the neuronal membrane through enzymatic actions, which in turn reinforces the activity of these immune cells [60]. The activation of microglia by nociceptive stimulation leads to their proliferation in the spinal cord dorsal horn, which, as in their peripheral counterparts, contributes greatly to the production of pro-inflammatory cytokines such as TNF, IL1-β and IL-6, and hence to the increased activity of central neurons to facilitate the central transmission of pain signals [22,42]. Furthermore, these pro-inflammatory cytokines, together with factors released by the central terminals of peripheral sensory neurons (such as ATP), promote astrocyte activation [46].

Astrocytes constitute networks interconnected by gap junctions, which contain hemichannels formed by connexins, e.g. connexin 43 (Cx43). The union of two hemichannels, one from each astrocyte, forms a complete channel. These channels allow a rapid exchange of ions and metabolites between astrocytes that constitute the network [61]. When astrocytes are activated by the signals described in the preceding

paragraph, they become hypertrophic, and Cx43 moves to places other than the gap junctions between astrocytes, which allows ATP and D-serine to leak into the extracellular environment [18,61]. D-serine is synthesized by an inducible racemase in the astrocyte. While ATP activates neuronal purinergic receptors, D-serine acts as a co-agonist (at the glycine-binding site) of NMDA receptors at central synapses [61]. Together, the activity of microglia and astrocytes contributes to the sensitization of central nociceptive pathways. Microglia activate earlier than astrocytes during chronic pain, and therefore it is hypothesized that while microglia are particularly relevant in early stages of pathological pain, astrocytes play a more important role in its maintenance [62]. However, astrocytes can be activated in response to brief (minutes) nociceptive stimuli by enhancing aromatase activity, which produces 17β-estradiol [63,64]. This product has a neuroprotective effect [65], although it also exerts pronociceptive actions [63].

While the evidence for the location of sigma-1 receptors in peripheral sensory neurons is clear, some immunohistochemical studies have shown an exclusively neuronal location of this receptor in the dorsal horn [66,67], while others have detected this receptor in astrocytes but not in neurons [68,69]. Therefore, there is no consensus on the exact location of sigma-1 receptors in the dorsal horn. The disparate findings may be due to the specificity of the antibodies used, as well as to the different staining procedures. More studies are needed to clarify the exact location of sigma-1 receptors in the spinal cord. Although the precise location of these receptors in the dorsal horn is not clear, the results of studies aimed at determining their role in central neuroinflammation are highly consistent, as will be described below.

A decrease in microgliosis in the spinal cord dorsal horn was seen after the preemptive administration (before pain and neuroinflammation were established) of a single dose of the sigma-1 antagonist BD-1047 in a model of acute inflammation in rats [67], and after repeated treatment with sigma-1 antagonists (BD-1047 or S1RA) in the early stages of development of chronic pain in models of osteoarthritis in mice [59], and bone cancer pain in rats [70]. The decrease in microgliosis induced by sigma-1 antagonism was accompanied by a decrease in pro-inflammatory cytokines of microglial origin, such as TNF or IL-1β [59,67]. In a mouse model of central neuropathic pain, a marked decrease was seen in the levels of these pro-inflammatory cytokines in sigma-1 receptor knockout mice or in wild-type mice after S1RA treatment [71,72]. In all these studies, the decrease in microglial activity or in pro-inflammatory cytokines in the dorsal horn induced by sigma-1 receptor inhibition was accompanied by a decrease in sensory hypersensitivity.

The repeated early administration of the sigma-1 receptor antagonist BD-1047 also prevented astrocytosis in the spinal cord dorsal horn in several pathological pain models. These include carrageenan inflammation in rats [73], peripheral neuropathic pain induced by mechanical injury to the sciatic nerve in mice [68], and a mouse model of central neuropathic pain [69]. In addition, sigma-1 receptor inhibition decreased the expression of serine racemase, with a consequent decrease in D-serine production [74], and connexin Cx43 expression [69], which may affect the release of chemical algogens by astrocytes at central synapses. In all these studies, a decrease in sensory hypersensitivity was seen in different pain models, indicating that the decrease in astrocyte activity by sigma-1 antagonism had functional repercussions. As noted above, D-serine acts as a co-agonist for NMDA receptors. Therefore, pain relief mediated by the inhibition of astrocyte activity by sigma-1 antagonism can be explained by a decrease in glutamatergic activity in the dorsal horn. In this connection, the intrathecal administration of the sigma-1 agonist PRE-084 was reported to increase the pronociceptive effects of NMDA, and this process was reversed by inhibitors of astrocyte activity [75]; these findings support the modulation of astrocyte-mediated glutamatergic pronociceptive effects by sigma-1 receptors. Finally, as an example of the role of sigma-1 receptors in the rapid pronociceptive effects of astrocytes, it was reported that intraplantar formalin triggered increased astrocyte aromatase activity within minutes of injection, and that this process was inhibited by sigma-1 antagonism [64].

Studies that explored the role of sigma-1 receptors in central neuroinflammation are summarized in Table 1.

It is important to note that all central processes in these chronic pain models (except those induced by direct injury to the spinal cord) are triggered by an initial peripheral nociceptive activity. As previously discussed, CCL-2 from peripheral sensory neurons plays an important role in microglial recruitment, and the activity of these immune cells is in turn important for the activation of astroglia. Given that the inhibition of sigma-1 receptors reduces the production of this chemokine in the DRG [53], it cannot be ruled out that at least part of the central effects of sigma-1 receptor inhibition described in this section are influenced by peripheral sigma-1 receptors. Even studies in which sigma-1 antagonists were administered intrathecally (see Table 1) may be influenced by peripheral actions of the drugs tested, given that in this type of experimental procedure the injected solution reaches the DRG [76].

Taken together, these results suggest that sigma-1 receptors play a highly relevant role in central neuroinflammation by modulating the activity of microglia and astrocytes in the spinal cord dorsal horn.

In addition to neuroinflammation in the spinal cord, it is known that during chronic pain, microglial activity increases in supraspinal areas, both in rodents [77,78] and humans [79]. Although the role of supraspinal neuroinflammation in pain is much less well studied than at the spinal cord level, it is believed to increase nociceptive transmission and pain perception [80]. Administration of the sigma-1 antagonist S1RA in animals with experimental osteoarthritis was reported to decrease microglial proliferation in the medial prefrontal cortex [78], which is relevant for emotional processing [81,82], cognitive function [83], and the modulation of pain perception [84,85]. Interestingly, sigma-1 antagonism not only decreased sensory hypersensitivity, but also improved cognitive deficits and depressive-like behaviors in these animals [78]. This research is summarized in Table 1. The results to date indicate that sigma-1 antagonism, possibly due to supraspinal modulation of the neuroinflammatory response, not only decreases simple reflex behaviors based on stimulus-response results indicative of sensory hypersensitivity [86], but is also able to alter deeper aspects of the pain experience.

5. Is prevention better than cure?

As described in the preceding sections, the studies showing that sigma-1 antagonism decreased peripheral and central neuroinflammation used a preemptive approach in which drug treatment was started before pain and neuroinflammation were fully established. Moreover, in the knockout mice used in these studies, the sigma-1 gene was constitutively inactivated, and therefore sigma-1 receptors were not expressed during pain induction. When viral vectors were used to decrease sigma-1 receptor expression during neuropathic pain, they were administered at the time of the nerve injury (see Table 1 for references). However, it has been shown that repeated administration of the selective sigma-1 antagonist S1RA was also able to induce ameliorative effects when sensory hypersensitivity was fully established in models of osteoarthritis [59] and neuropathic pain of different etiologies [87–89]. It is thus likely that this later treatment with a sigma-1 antagonist would also be able to decrease markers of neuroinflammation, although this remains to be tested.

It is important to note that the acute systemic administration of S1RA also ameliorated sensory hypersensitivity when chronic pain was fully established in a model of osteoarthritis [59] and several types of neuropathic pain [58,88–92]. If the prevention or reversion of neuroinflammation were the only mechanism by which sigma-1 receptor inhibition decreased pain behavior in these pain models, acute sigma-1 antagonism would not be expected to produce a robust effect once neuroinflammation was fully developed. We recently reported, as summarized in Table 1, that the ameliorative effect of the acute systemic

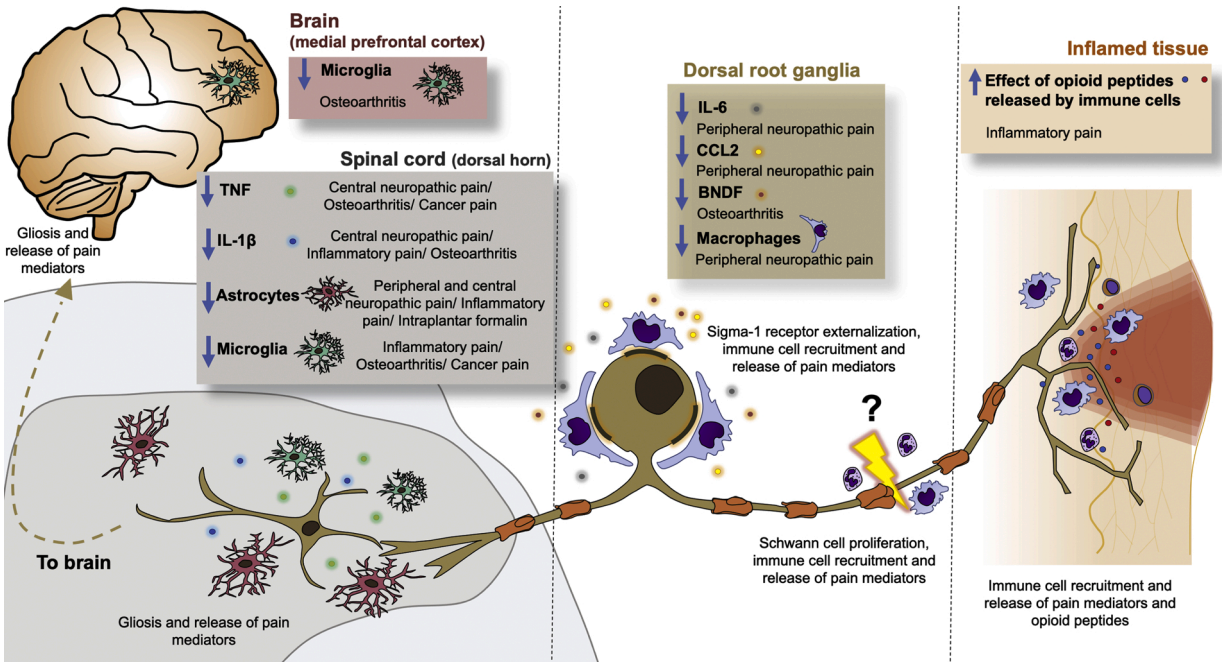

Fig. 1. Effect of sigma-1 receptor inhibition on neuroimmune and neuroglial interactions in pain. Neurons and non-neuronal cells interact through chemical signals at several steps of nociceptive transmission. The colored boxes summarize the effects of sigma-1 receptor inhibition and the preclinical pain models in which they have been described. The effect of sigma-1 receptor inhibition in Schwann cells is unknown (although these cells express this receptor), and this gap in our knowledge is indicated with a question mark. See references in the text and in Table 1 for further information.

administration of S1RA on neuropathic pain was reversed by the peripheral opioid antagonist naloxone methiodide [58]. Considering the abundance of immune cells in the peripheral nervous system during neuropathic pain (and other types of chronic pain), and that immune cells produce endogenous opioids [4], it seems reasonable to posit that the inhibition of sigma-1 receptors enhances immune-driven opioid analgesia during neuropathic pain, in consonance with the findings discussed in section 2 regarding inflammatory pain. In summary, it is clear that sigma-1 antagonism can be beneficial even when chronic pain states are fully developed.

6. Does the modulation of neuroinflammation by sigma-1 receptors differ between sexes?

Traditionally, in preclinical research and particularly in neurosciences, the use of female animals has been almost completely avoided [93]. This is particularly relevant for pain research, since a large part of chronic pain disorders are, in general terms, more prevalent in women than in men [94]. Therefore the need to study pain processing in both sexes is clear. Furthermore, it was recently found that the role of neuroinflammation in pain may be different between animals of each sex (at least in mice). Specifically, it is thought that microglia play a more relevant role in neuropathic pain in male animals than in females, whereas T-cells play a more relevant role in females than in males [95]. Regarding the research articles reviewed here, although more studies used male than female animals (see Table 1) and no formal comparison between males and females was reported in any individual study, sigma-1 receptor inhibition appears to curtail neuroinflammatory processes in both sexes.

Some previous studies evaluated the effect of sigma-1 receptor inhibition on pain modulation in animals of both sexes. Specifically, sigma-1 receptor knockout mice of both sexes showed equivalent losses of sensitivity to capsaicin-induced mechanical allodynia (a behavioral model of central sensitization) [96]. It was further reported that there were no differences between sexes, either in mutant animals or in wild-type mice treated with S1RA, in hypersensitivity to a mechanical, heat or cold stimulus in a model of peripheral neuropathic pain [58]. Therefore, at present there is no evidence to suggest the existence of sex-dependent differences in pain modulation by sigma-1 receptors. It should be noted that although sexual dimorphism can be expressed as a difference in pain sensitivity, this is not always the case given that mechanistic differences between sexes have been observed despite the fact that sensitivity to the painful stimulus was identical in males and females [86]. Therefore, it cannot be ruled out that there may be as yet unidentified parameters of sexual dimorphism in the role of sigma-1 receptors as modulators of the communication between sensory neurons and immune or glial cells.

7. Clinical trials with the selective sigma-1 antagonist S1RA

S1RA is a selective sigma-1 receptor antagonist developed by Esteve Pharmaceuticals S.A. in collaboration with several research groups, including our own group. As discussed in previous sections, antagonism of sigma-1 receptors by S1RA (and by other sigma-1 ligands) induces ameliorative effects on pain in animal models of inflammation, central and peripheral neuropathy, osteoarthritis, and cancer. At least some of these effects can be attributed to the potentiation of immune-driven opioid analgesia, the modulation of central and peripheral neuroinflammatory responses, or both mechanisms.

Three independent phase 1 clinical trials involving a total of 174 individuals showed S1RA to have a good safety profile in healthy people [97]. In addition, S1RA has been tested in a phase 2a clinical trial for the treatment of neuropathic pain induced by oxaliplatin [98], a widely used antineoplastic which induces the development of peripheral neuropathy in a high percentage of patients [99]. In this study, patients received preemptive treatment with S1RA, which was given during the first 5 days of each chemotherapy cycle [98]. S1RA decreased hypersensitivity to a cold stimulus, as well as the percentage of patients who experienced severe chronic neuropathy. However, although the results are undoubtedly promising, the number of participants was small (62 patients treated with S1RA) [98]. Therefore, more studies are needed to more thoroughly evaluate the analgesic potential of S1RA in

oxaliplatin-induced neuropathic pain.

Preclinical studies have shown that S1RA is able to inhibit the development of peripheral neuropathy induced not only by oxaliplatin [88], but also by the antineoplastic drugs paclitaxel [91,100], cisplatin and vincristine [92]. However, the modulation of neuroinflammatory processes by sigma-1 receptors in neuropathic pain induced by antineoplastics has not been studied to date. Neuroinflammation during this particular type of neuropathy does not appear to be as robust as that produced after traumatic nerve damage, and the mechanisms appear to not be fully overlapping between the different chemotherapeutics employed. For instance, microgliosis seems to predominate in paclitaxel-induced neuropathic pain, whereas astrocytosis appears to be more relevant in oxaliplatin-induced neuropathy [99]. Therefore, additional studies are needed to determine the mechanism by which S1RA inhibits neuropathic pain induced by antineoplastic drugs.

A final consideration is that given the safety profile of S1RA in clinical trials, and the robust ameliorative effects of this drug in animal models of pain of different etiology, further clinical trials in patients with other types of painful disorders (in addition to chemotherapy-induced neuropathic pain) appear to be fully warranted.

8. Conclusions

We have summarized the current scientific evidence that the inhibition of sigma-1 receptors increases the peripheral opioid analgesia induced by immune cells, and decreases peripheral and central neuroinflammation in several models of pathological pain. Although the original research reviewed here was carried out in a variety of pain models covering very specific aspects of the overall process, the findings, when taken together, support the conclusion that sigma-1 receptors play a key role in the communication between neurons and non-neuronal cells at several key steps in painful neurotransmission (see Fig. 1). In light of the relevance of the interactions between sensory neurons and non-neuronal cells in chronic pain, sigma-1 antagonists may constitute a new class of analgesics with an unprecedented mechanism of action. We look forward to new preclinical and clinical studies focused on exploring the therapeutic possibilities of these intriguing receptors.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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