TARGETING IMMUNE-DRIVEN OPIOID ANALGESIA BY SIGMA-1 RECEPTORS: OPENING THE DOOR TO NOVEL PERSPECTIVES FOR THE ANALGESIC USE OF SIGMA-1 ANTAGONISTS

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Abstract

Immune cells have a known role in pronociception, since they release a myriad of inflammatory algogens which interact with neurons to facilitate pain signaling. However, these cells also produce endogenous opioid peptides with analgesic potential. The sigma-1 receptor is a ligand-operated chaperone that modulates neurotransmission by interacting with multiple protein partners, including the μ-opioid receptor. We recently found that sigma-1 antagonists are able to induce opioid analgesia by enhancing the action of endogenous opioid peptides of immune origin during inflammation. This opioid analgesia is seen only at the inflamed site, where immune cells naturally accumulate. In this article we review the difficulties of targeting the opioid system for selective pain relief, and discuss the dual role of immune cells in pain and analgesia. Our discussion creates perspectives for possible novel therapeutic uses of sigma-1 antagonists as agents able to maximize the analgesic potential of the immune system

Keywords: sigma-1 receptors; endogenous opioid peptides; analgesia; immune cells; neuro-immune interactions

Abbreviations

CRF, corticotrophin-releasing factor; DRG, dorsal root ganglion; EOPs, endogenous opioid peptides; ICAM-1, intercellular adhesion molecule-1; IL-1, interleukin-1

1. Introduction: the need for new analgesics

Pain affects approximately 20% of the adult population, with millions of people suffering from chronic pain of diverse etiology, including inflammatory or neuropathic pain [1,2]. Many patients suffer from unrelieved or undertreated pain, since current medications (including opioids, nonsteroidal anti-inflammatory drugs and gabapentinoids) show limited efficacy or a range of side effects (or both) that strongly limit their use; hence the importance of identifying new pharmacological targets for pain relief. In spite of increasing efforts by basic and clinical pain researchers, most "new" pain medications consist of refined delivery methods for known analgesic drugs, or combination therapies based on agents with distinct targets and non- overlapping side effect. Reports of analgesics aimed at novel pharmacological targets with truly new mechanisms of action thus remain scarce [3,4].

The sigma-1 antagonist S1RA (also known as MR309) is one of the very few exceptions in this context: this recently developed first-in-class analgesic drug has shown encouraging results in a phase IIa clinical trial for neuropathic pain [5]. In this article we summarize the peculiarities of the sigma-1 receptor as a pharmacological target, and discuss the possible indications for analgesia of sigma-1 antagonists in light of the recently described modulation of immune-driven endogenous opioid analgesia by these receptors. Our discussion is situated in the context of the difficulties of targeting the opioid system with opioid drugs to induce selective pain relief, and the known role of immune cells in pain and analgesia.

2. Sigma-1 receptor: a unique pharmacological target

The classical pharmacological receptors include G protein-coupled receptors, ion channels, transporters, receptors linked to enzymatic activity, enzymes *per se*, and nuclear hormone receptors, which together constitute almost the entire set of current drug targets [6,7].

The sigma-1 receptor is a single polypeptide composed of 223 amino acids with no homology to any known mammalian protein (reviewed in [8]), and as opposed to the standard pharmacological receptors noted above, the sigma-1 receptor is a Ca^{2+}-sensing chaperone [9].

At the subcellular level, sigma-1 receptors are found in particularly high densities in mitochondrion-associated endoplasmic reticulum membranes [9]. In stress situations, sigma-1 receptors translocate to other areas of the cell, such as the plasmalemmal area within the endoplasmic reticulum network, or the plasma membrane itself, allowing their physical interaction with different membrane targets [10]. The membrane targets of sigma-1 receptors include several ion channels and GPCRs. The ion channels known to interact with sigma-1 receptors are NMDA receptors, voltage-dependent K+ channels (Kv1.2, Kv1.3, Kv1.4 and Kv1.5), L-type voltage-dependent Ca2+ channels, acid-sensing ion channels of the 1a subtype, and GABAA receptors. The GPCRs known to be targeted by sigma-1 receptors are μ-opioid receptors, dopamine D1 and D2 receptors, cannabinoid receptor 1, and serotonin receptors 1A and 2A (reviewed in [10,11]). Once sigma-1 receptors interact with their protein partners, they act as a regulatory subunit and have a profound impact on the regulation of neurotransmission (reviewed in [10,11]). The complete interactome of sigma-1 receptors is almost certainly far from being fully discovered, and much research is still needed to obtain a complete picture of all possible neuromodulatory actions of these receptors. The interaction of sigma-1 receptors with

their protein partners is Ca2+-dependent [12]. Therefore, sigma-1 receptors probably do not interact simultaneously with all their protein partners when they translocate, but may be directed to specific membrane targets by the local Ca2+ microenvironment, which in turn is dependent on the activation state of the protein partner involved. Hence, due to the chaperoning nature of sigma-1 receptors, they do not have a single mechanism of action but may rather impact several neuromodulatory pathways through their many protein partners. In light of these unprecedented neuromodulatory actions of sigma-1 receptors, they can be considered a unique pharmacological target.

Fortunately, sigma-1 receptors are drugable proteins, which facilitates functional studies and the development of selective sigma-1 ligands with potential clinical applications. Currently, both selective sigma-1 agonists and antagonists are available [8,13,14]. Among these, the sigma-1 antagonist S1RA has been shown to exhibit exquisite selectivity for sigma-1 receptors, while lacking affinity for 170 additional drug targets [14].

3. The physiological role of the opioid system and the difficulty of targeting selective pain relief with opioid drugs

Enkephalins were the first endogenous opioid peptides (EOPs) to be discovered, in 1975 [15]. It was later shown that they are not the only EOPs, with the discovery of endorphins dynorphins and endomorphins (reviewed in [16]). Although EOPs were initially reported to be produced in the central nervous system, they can also be found in peripheral tissues such as in the gastrointestinal tract [17]. Currently, EOPs are known to play important physiological roles by acting on μ, δ and κ opioid receptors, with varying selectivity for each opioid receptor subtype depending on the particular EOP [16,18]. This endogenous opioid system participates in pain modulation, and it is thought that many if not most nonpharmacological therapies for pain, including acupuncture, exercise, and some mind-body interventions (such as mindfulness meditation or the placebo effect), work by engaging endogenous analgesic pathways that are at least partly opioid dependent [19,20,21,22,23]. In fact, morphine, initially found to be the active compound of opium extract, as well as all other opioid agonists (both naturally-occurring and synthetic), exert their analgesic effects by mimicking the actions of EOPs, but at a much higher intensity than that achievable by nonpharmacological interventions. The actions of opium and its derivatives on this important endogenous analgesic system account for their centuries-long history as gold standard analgesics. In the 17th century Thomas Sydenham, known as the "English Hippocrates", wrote, "Of all the remedies it has pleased almighty God to give man to relieve his suffering, none is so universal and so efficacious as opium".

However, in addition to pain modulation, the endogenous opioid system also participates, mainly via the central nervous system, in the regulation of many other aspects of physiology including respiration, rewarding behavior, social bonding, mood, stress responses, learning and memory as well as endocrine functions (reviewed in [17,22,24,25,26]). In addition, this system is involved in peripheral processes, e.g. in the regulation of gastrointestinal transit (reviewed in [17,24]). It is important to note that in addition to the analgesic properties of opioid drugs, they alter the complex endogenous neuromodulatory system and can potentially induce a plethora of undesirable nonanalgesic effects. Among the effects produced centrally are respiratory depression, dependence, mood changes, sedation, memory and learning impairment, and even endocrine dysfunction [27,28,29,30]. The effects mediated at peripheral levels include opioid- induced constipation [28]. Pharmacologists in different countries have

attempted to increase the therapeutic range of opioid drugs (i.e. to improve the analgesia/adverse events ratio), and although this has been partially achieved with new opioid formulations (e.g. [31]) and with the development of opioid agonists biased toward analgesic pathways (reviewed in [32]), the analgesic effects of opioid drugs appear to be difficult to dissociate from their worrisome unwanted effects, given that they act simultaneously on the somatosensory system and on all other systems which are naturally modulated by EOPs.

4. The dual analgesic/proalgesic role of immune cells: the balance between endogenous opioid peptides and algogenic chemicals

Although EOPs have been classically thought to be produced by neurons, in 1990 it was shown that they can also be produced by immune cells [33]. The interaction between immune cells and pain, particularly during peripheral inflammation, has been an intense focus of research in recent decades. Neutrophils, macrophages and lymphocytes have all been reported to produce EOPs [34,35] and opioid peptides derived from immune cells include β-endorphin, enkephalins, dynorphins and endomorphins [36,37,38]. However, not all individual immune cells produce the same EOPs, even among immune cell subtypes. For example, the population of macrophages which express endomorphin-1 only partially overlaps with the population that expresses dynorphin [39]. The main source of EOPs in inflamed tissues is believed to be immune cells [36,40], and because the predominant immune cell types vary during the time course of inflammation [36,41,42,43], distinct leukocyte lineages are likely to contribute to the of EOPs present at the inflamed site during different stages of inflammation.

Inflammation establishes a particular environment that leads to the enhancement of peripheral opioid effects. Under inflammatory conditions there is an increase in the synthesis and axonal transport of opioid receptors from dorsal root ganglia (DRG) neurons to their peripheral terminals [44,45], together with a decrease in local pH. This decrease in turn favors opioid agonist efficacy by enhancing the efficiency of coupling between opioid receptors and G proteins [46,47]. Moreover, inflammation induces the sprouting of sensory nerve terminals and disruption of the perineurial barrier, thus facilitating access of opioid agonists to their receptors [48]. These conditions may enhance the analgesic potential of immune cells containing EOPs, which naturally accumulate at the inflamed site. In addition, opioid peptide expression is increased in activated immune cells compared to quiescent leukocytes [38,49], and this expression may enhance the analgesic potential of these cells. However, in addition to EOPs, immune cells have been shown to produce a wide variety of algogenic chemicals such as nerve growth factor, tumor necrosis factor, IL-1 β, IL-6, histamine, and arachidonic acid derivatives including prostaglandin E2, (5,6-epoxyeicosatrienoic acid and hydroxyeicosatetraenoic acid (among many others) [50,51]. All these substances are able to promote pain by acting on peripheral nerve terminals in the inflamed tissue [50,51].

Interestingly, ICAM-1 (intercellular adhesion molecule-1)– a molecule present in endothelial cells, where it plays a key role in the process leading to leukocyte extravasation [34,37] – is also expressed in peripheral nerve terminals [34]. The expression of neuronal ICAM-1 facilitates the physical interaction of a portion of leukocytes in the inflamed site with nerve endings [34]. Close proximity between immune cells and peripheral nerve terminals may be needed for the actions of EOPs of immune origin, which would otherwise be rapidly inactivated by increased proteolytic activity at the inflamed site [34]. However, the proximity between immune cells and

peripheral nerve terminals might also facilitate the proalgesic role of the former, and one possible result is the simultaneous, dual analgesic/proalgesic modulation of nociceptive neurotransmission by the cross-talk between the immune and peripheral nervous system due to the concurrent release of EOPs and algogenic chemicals by immune cells. It is worth noting that in spite of the analgesic potential of EOPs of immune origin, it is well known that inflammation leads to pain. In this connection, a pronociceptive role for immune cells has been documented in several rodent models of inflammatory pain [42,43], and during incisional pain (a rodent model of postoperative pain), which is accompanied by an inflammatory reaction at the wound site [42].

In addition to EOP production by peripheral immune cells, it is also known that microglia, the macrophages of the central nervous system, can also produce EOPs [52]. In rodent models of chronic inflammation, such as during experimentally-induced chronic arthritis, the massive proliferation of microglia in the spinal cord contributes to pain development and maintenance [53,54]. Similarly, peripheral nerve injury also triggers massive immune cell infiltration or proliferation not only in the injured nerve, but also in the affected DRG and the spinal cord, where immune cells facilitate pain signaling [55,56]. These findings are evidence that EOP activity during pathological pain is not enough to fully counterbalance the effects of the myriad of proalgesic agents released by immune cells in pathological situations tested thus far, and that as a result, the balance between the analgesic and proalgesic effects of immune cells is normally shifted toward pronociception. However, immune-mediated peripheral opioid analgesia (sensitive to the opioid antagonist naloxone) can be unmasked by stress conditions such as cold water swimming [33,57,58,59]. This analgesia can be mimicked by the administration of corticotrophin-releasing factor (CRF), a key molecule produced in response to emotional stress [60], which stimulates the secretion of EOPs from immune cells [61,62]. Although CRF cannot readily be used as an analgesic, since it is one of the main mediators of fear and anxiety behaviors [63,64], the research summarized above elegantly illustrates that EOPs of immune origin have analgesic potential that could be exploited.

5. Sigma-1 receptors and pain: from the modulation of morphine antinociception to the control of immune-driven opioid analgesia

The first description of the role of sigma-1 receptors in pain date to the early 1990s, when Chien and Pasternak studied the effects on morphine antinociception of haloperidol – a prototypical sigma antagonist at a time when no selective sigma drugs were available. They found that haloperidol enhanced morphine antinociception [65,66], and were the first to suggest the existence of a tonically active anti-opioid sigma-1 system. Because opioid analgesia is classically thought to be more prominent at central levels [67,68], later studies focused on the central modulation of opioid analgesia by sigma-1 receptors. It was found that sigma-1 inhibition markedly enhances morphine-induced antinociception in the brainstem, via modulation of the descending pain modulatory system [69]. More recently, we found that sigma-1 antagonism at peripheral levels was also able to markedly enhance morphine antinociception [70,71]. Therefore, the tonically active anti-opioid sigma-1 system operates not only at central levels, but also at peripheral sites. In fact, the density of sigma-1 receptors in the DRG was found to be much higher than in brainstem areas or the dorsal spinal cord [71], pointing to a prominent role for peripheral sigma-1 receptors in pain modulation. The increase in morphine antinociception by sigma-1 inhibition is also seen with other clinically relevant μ-opioid drugs such as buprenorphine, oxycodone or fentanyl [71,72].

The molecular mechanism of the interaction between sigma-1 receptors and the μ-opioid receptor was recently elucidated. Sigma-1 antagonism increases μ-opioid signaling [73] through complex regulation of the interaction between NMDA receptors and μ-opioid receptors, two of the main protein targets of sigma-1 receptors [12,74]. Although physical interaction between sigma-1 receptors and opioid receptors has been reported only for the μ-opioid subtype, sigma-1 antagonists are also known to enhance the analgesic effects induced by selective κ or δ opioid agonists [11], suggesting that sigma-1 receptors can interact with all opioid receptor subtypes and not exclusively with μ-opioid receptors. In addition to opioid receptors, other protein targets of sigma-1 receptors are known to participate in opioid analgesia. For example, L-type Ca^{2+} channels are among the downstream effectors of opioid signaling [28]. Therefore, the enhancement of opioid analgesia by sigma-1 antagonism may be the result of simultaneous interactions between several membrane targets of sigma-1 receptors, and not only of the direct modulation of opioid–NMDA receptors.

In addition to opioid antinociception, the possible modulation of opioid-induced adverse (nonanalgesic) events by sigma-1 receptors has been also tested. In contrast to the modulation of opioid antinociception by sigma-1 receptors, selective sigma-1 drugs did not alter opioid-induced lethality (suggesting no alterations in opioid-induced respiratory depression), tolerance, physical dependence (withdrawal syndrome) or constipation [66,70,71,75]. Regardless of the exact mechanisms underlying the differential modulation of opioid antinociception and adverse events by sigma-1 receptors (which are unclear at the moment), these findings point to selective modulation of opioid sensory effects by sigma-1 receptors.

Although it has long been clear, as noted above, that sigma-1 receptors strongly modulate the analgesic effects induced by opioid drugs, it was only recently that evidence of the modulation of endogenous opioid analgesia by sigma-1 receptors was reported. During an inflammatory insult, the antagonism of sigma-1 receptors by several sigma-1 drugs, including the selective sigma-1 antagonists S1RA and BD-1063, was able to reverse hyperalgesia induced by inflammatory substances [43,76,77,78,79], and this effect was recently found to be mediated peripherally and sensitive to naloxone [43]. Both S1RA and BD-1063 lack affinity for opioid receptors [14,70], and therefore their effects are not due to direct opioid actions. Furthermore, these opioid-like sigma-1 analgesic effects were dependent on the presence of EOP-producing immune cells at the site of inflammation: the depletion of immune cells at this site reversed the effects of sigma-1 antagonism [43]. Therefore, although immune cells have predominantly pronociceptive actions as noted above, sigma-1 antagonism is able, by disinhibiting the endogenous opioidergic system, to alter the neuromodulatory actions of the immune system and thus to shift the balance between the proalgesic/analgesic effects toward analgesia (see Fig. 1).

Immune cells can harbor a variety of EOPs, as described in the preceding section. Although it is not yet known which EOPs are modulated by sigma-1 receptors, the fact that this chaperone protein is able to modulate the analgesic effects induced by μ, κ or δ opioid drugs (reviewed in [11]) makes it likely that sigma-1 antagonism can enhance the analgesic effects of all EOPs regardless of their selectivity for different opioid receptor subtypes.

It is worth pointing out that although sigma-1 antagonists induce opioid analgesia during inflammation by enhancing the effects of EOPs of immune origin, these drugs lack the typical side effects induced by opioids such as morphine. For example, sigma-1 antagonism does not have addiction potential, and does not induce changes in pupil

size or gastrointestinal transit [70,71,75]. These results suggest that sigma-1 antagonism enhances the sensory effects of EOPs without affecting the endogenous opioid system as a whole, in contrast to opioid drugs – which induce a myriad of nonanalgesic side effects because of their marked stimulation of the opioid system. This effect of sigma-1 antagonists may be related to both the sensory selectivity of the modulation of opioid effects by sigma-1 receptors, and the accumulation of EOPs harbored by immune cells at the site of injury. In fact, the analgesic effects of sigma-1 antagonists are only detected at the inflamed site, and these compounds do not induce generalized analgesia [43], in contrast to opioid drugs. Therefore, EOP-mediated analgesia induced by sigma-1 antagonism during inflammation differs markedly from the analgesic effect of opioid drugs.

6. Possible therapeutic opportunities for the enhancement of immune-driven opioid analgesia by sigma-1 receptors

The most obvious option for clinical applications of the potentiation of immune-driven opioid analgesia by sigma-1 antagonists is of course pain relief during inflammatory diseases.

Among the painful inflammatory diseases that would benefit from improved symptomatic treatments are the several known types of arthritis, which are highly prevalent and sometimes clinically challenging to treat. The etiology of inflammatory arthritis is diverse, and includes gouty arthritis, the most common inflammatory arthritis in the Western world [80], psoriatic arthritis [81], and of course the types of inflammatory arthritis that are due to autoimmune diseases, such as rheumatoid arthritis [82,83] or arthritis in patients with systemic lupus erythematosus [84,85]. These diseases are characterized by a prominent immune infiltrate, and so may be appropriate targets for treatments based on increased immune-driven opioid analgesia by sigma-1 antagonism. In contrast, other types of arthritis such as osteoarthritis, in which the immune infiltrate is not as prominent as in inflammatory arthritis (and therefore involves potentially lower numbers of EOP-containing immune cells), might be less susceptible to the ameliorative effects of sigma-1 antagonists via this mechanism. In fact, the levels of β-endorphin in synovial fluid from patients with osteoarthritis is known to be lower than in patients with rheumatoid arthritis [86]. However, patients with osteoarthritis have – surprisingly – higher numbers of immune cells harboring endomorphins in the synovial tissue than patients with rheumatoid arthritis [87]. It is therefore difficult to predict whether sigma-1 antagonism would be more beneficial for pain treatment in patients with either type of arthritis. Another clinical condition that might be ameliorated by enhancing immune-driven opioid analgesia through sigma-1 antagonism is postsurgical pain, since after injury immune cells accumulate in the wound and remain there until the tissue is fully repaired, at which time when the inflammatory reaction (and consequent pain) resolves [42,88]. In this connection, the wound fluid from patients after surgical procedures is known to contains immune cells harboring EOPs [89].

Sigma-1 antagonism ameliorates capsaicin-induced visceral pain [90], indicating that in addition to somatic tissues, sigma-1 receptors are also active in the viscera. These latter tissues can also be the site of painful inflammatory conditions with a marked immune component, such as inflammatory bowel disease (Crohn's disease and ulcerative colitis) [91]. Thus, patients with these conditions might also benefit from this type of therapy, for the same reasons as noted above with regard to the accumulation of immune cells

in the painful area. However, pain in patients with irritable bowel syndrome, in which both the number of macrophages/monocytes and the β-endorphin content are reduced in colonic samples in comparison to healthy people [92], may derive limited benefits from therapies to potentiate immune-driven peripheral opioid analgesia by sigma-1 antagonism.

Interestingly, research in models of central sensitization after the injection of algogenic chemicals, such as secondary mechanical allodynia after intraplantar capsaicin- or formalin- induced pain, showed that the antinociceptive effects of sigma-1 antagonists are not reversed by naloxone [43,93], and therefore do not depend on opioid activation. It is worth pointing out that both models are based on strong, rapid C-fiber activation, which leads to early central sensitization within a few minutes and thus obviates the possibility of immune cell recruitment, which requires longer times. In fact, sigma-1 receptors are known to modulate the sensitization of central neurons [14,94,95], and this may explain the results obtained in the behavioral models noted above. These studies showed that sigma-1 receptors are able to regulate neuronal sensitization by modulating pathways other than the endogenous opioid system.

Taking into account the wide variety of protein partners of sigma-1 receptors that can influence neurotransmission (as described in the Section 2 "Sigma-1 receptor: a unique pharmacological target"), it is not surprising that sigma-1 antagonists can modulate neurotransmission in opioid-dependent and -independent pathways. Central sensitization plays a pivotal role in the development and maintenance of neuropathic pain [96], and overwhelming evidence of the ability of sigma-1 receptors to modulate central sensitization has encouraged the development of the selective sigma-1 antagonist S1RA [14]. This compound ameliorates neuropathic pain of diverse etiology in rodents [14,97,98], and has yielded promising results in a phase IIa clinical trial in patients with oxaliplatin-induced neuropathic pain [5]. However, neuropathic pain (in contrast to simpler and faster experimental models of pain based on the injection of algogenic chemicals) is strongly influenced by microglial activation in the spinal cord dorsal horn and supraspinal structures, which sensitize central pain pathways [96,99], as well as by the interaction between the immune and the peripheral nervous system [55,56]. It is known that both microglia at central levels and immune cells infiltrating the injured nerve can produce EOPs [100,101,102]. Therefore, although sigma-1 receptors modulate central sensitization by their direct actions on neurons, the potentiation of the effects of immune-derived EOPs at central or peripheral levels (or both) might also contribute to the effects of sigma-1 antagonists on neuropathic pain.

7. Conclusions and final remarks

This Perspectives article summarizes and synthesizes current evidence on the dual proalgesic/analgesic role of immune cells. In light of recent evidence of the role of sigma-1 This Perspectives article summarizes and synthesizes current evidence on the dual proalgesic/analgesic role of immune cells. In light of recent evidence of the role of sigma-1 immune cells, our discussion raises perspectives for potential novel therapeutic uses of sigma-1 antagonists as analgesics able to influence the communication between immune cells and neurons in a way that results in opioid analgesia at inflamed sites, where immune cells accumulate. Although the sigma-1 antagonist S1RA has been developed with an intended primary indication for neuropathic pain, based at least partially on the prominent role of sigma-1 receptors on central sensitization, we believe that sigma-1 antagonists may also be useful in a variety of painful inflammatory diseases

thanks to their ability to enhance immune-driven endogenous opioid analgesia. In addition, given the massive immune infiltration during neuropathic pain at different levels of the somatosensory system, this immune-driven opioid analgesia may participate in the well known effects of sigma-1 antagonists in this type of pain, although this hypothesis remains to be tested. Of particular interest is the finding that not all analgesic effects of sigma-1 antagonists depend on activation of the endogenous opioid system – suggesting that sigma-1 receptors impact on neurotransmission via multiple mechanisms, which thus far have been only partially elucidated. We eagerly await future preclinical and clinical studies designed to explore the new analgesic potentialities of sigma-1 receptors.

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FIGURE

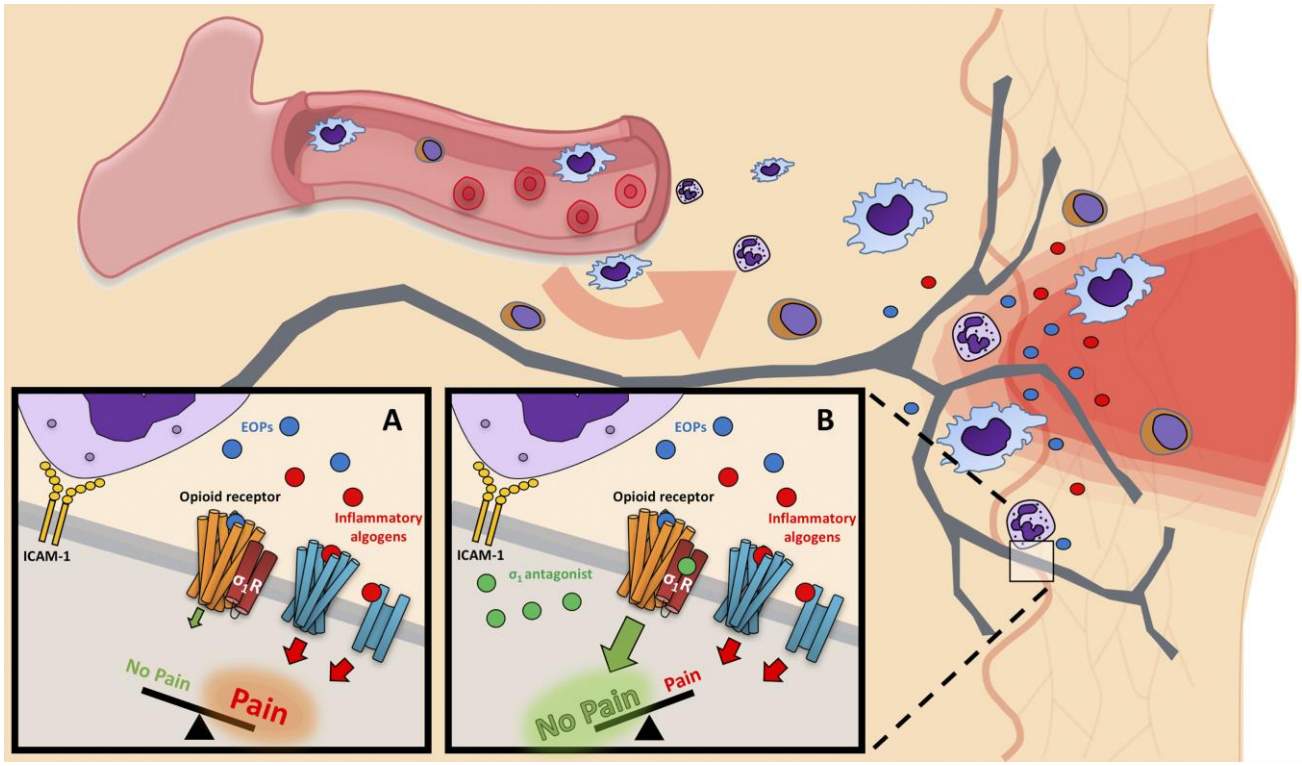

Figure 1. Effect of sigma-1 antagonism on immune-driven opioid analgesia. Immune cells migrate to the inflamed tissue, where they interact with peripheral nerve terminals which express ICAM-1 (intercellular adhesion molecule-1). These immune cells release both inflammatory algogens which promote pain, and endogenous opioid peptides (EOPs). Under normal conditions the overall result of this immune–neuron interaction is pain, because sigma-1 receptors (σ_1R) tonically inhibit opioid receptors, and hence decrease the analgesic effect of EOPs (A). In the presence of a sigma-1 antagonist, the effects of opioid receptors are enhanced, potentiating the effects of EOPs of immune origin, and resulting in immune-driven opioid analgesia (B).