Pharmacological Modulation of the Sigma 1 Receptor and the Treatment of Pain

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Abstract

There is a critical need for new analgesics acting through new mechanisms of action, which could increase the efficacy with respect to existing therapies and reduce their unwanted effects. Current preclinical evidence supports the modulatory role of sigma-1 receptors (σ_1R) in nociception, mainly based on the pain-attenuated phenotype of σ_1R knockout mice and on the antinociceptive effect exerted by σ_1R antagonists on pains of different etiologies. σ_1R is highly expressed in different pain areas of the CNS and the periphery (particularly dorsal root ganglia), and interacts and modulates the functionality of different receptors and ion channels. The antagonism of σ_1R leads to decreased amplification of pain signaling within the spinal cord (central sensitization), but recent data also support a role at the periphery. σ_1R antagonists have consistently demonstrated efficacy in neuropathic pain, but also in other types of pain including inflammatory, orofacial, visceral, and post-operative pain. Apart from acting alone, when combined with opioids, σ_1R antagonists enhance opioid analgesia but not opioid-induced unwanted effects. Interestingly, unlike opioids, σ_1R antagonists do not modify normal sensory mechanical and thermal sensitivity thresholds but they exert antihypersensitive effects in sensitizing conditions, enabling the reversal of nociceptive thresholds back to normal values. Accordingly, σ_1R antagonists are not strictly analgesics; they are antiallodynic and antihyperalgesic drugs acting when the system is sensitized following prolonged noxious stimulation or persistent abnormal afferent input (e.g., secondary to nerve injury). These are

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distinctive features allowing σ_1R antagonists to exert a modulatory effect specifically in pathophysiological conditions such as chronic pain.

Keywords
Analgesia • Antinociception • Chronic pain • Sigma-1 receptor • Opioid adjuvant • E-52862

8.1 Introduction

Acute pain has evolved as a key physiological alert system for avoiding noxious stimuli and protecting damaged regions of the body by discouraging physical contact and movement [1]. Conversely, chronic pain has been recognized as pain that persists past normal healing time and hence lacks the acute warning function of physiological nociception. Usually pain is regarded as chronic when it lasts or recurs for more than 3–6 months. Chronic pain may be associated with many common diseases or be a disease by itself. It can be debilitating, with those affected typically suffering psychological disturbance and significant activity restrictions. Chronic pain is a frequent condition, affecting an estimated 20 % of people worldwide and accounting for 15–20 % of physician visits [2]. Unfortunately, currently available treatments provide modest improvements in pain and minimum improvements in physical and emotional functioning [3]. Thus, the unmet medical need in the pain research area is huge, and particularly relevant in difficult-to-treat pain modalities, such as neuropathic pain.

Therefore, there is an urgent need to better understand the cellular and molecular mechanisms that mediate chronic pain and to use this knowledge to discover and develop improved therapeutics, especially new drugs acting through new mechanisms of action. Despite very intensive research efforts have translated into exponential growth of pain-related publication productivity and improvements in the understanding of pain mechanisms, those efforts have not yet yielded new analgesics. The most notable therapeutic advances have not been the development of novel evidence-based approaches, but rather changing trends in applications and practices within the available clinical armamentarium. In the absence of real breakthroughs in analgesic drug development, the landscape is dominated by incremental improvements of existing therapies [4], including combination treatments, new formulations of existing drugs, me-too drugs and refinements based on validated mechanisms. Opioids (moderate/severe pain), non-steroidal anti-inflammatory drugs (mild/moderate pain), triptans (migraine), and some anticonvulsants and antidepressants (neuropathic pain) account for the major analgesic classes. Most of them are old or even ancient discoveries and exert modest analgesic effect and/or are limited by their adverse effects, particularly when used chronically [5].

The sigma-1 receptor (σ_1R), a unique ligand-regulated chaperone protein with no precedent and no homology to known proteins [6], has become one among the new and most promising pharmacological targets in pain. Several studies have shown that inhibition of σ_1R leads to decreased amplification of pain signaling within the CNS. Indeed, σ_1R is expressed in several areas of the CNS specialized in nociceptive signaling processing, including the dorsal spinal cord, thalamus, periaqueductal gray (PAG), basolateral amygdala and rostroventral medulla (RVM) [7, 8]. σ_1R is also expressed in peripheral tissues including dorsal root ganglia (DRG) neurons [9, 10]. Importantly, its high density in DRG, in which σ_1R expression is roughly an order of magnitude higher than in several CNS areas involved in pain signaling, points to a functional role of peripheral σ_1R in pain modulation [11]. It is expressed by both sensory neurons and satellite cells in rat DRGs and its expression is downregulated in axotomized neurons and in accompanying satellite glial cells [10].

The use of the σ_1R knockout (KO) mice has been critical to identify the σ_1R as a modulator of

activity-induced sensitization of pain pathways. The σ_1R KO mice is insensitive or shows attenuated expression of pain behaviors in chemically-induced (e.g. formalin, capsaicin) and neuropathic pain models [12–19]. These genetic as well as pharmacological findings using several σ_1R ligands (see [20] for a review) provided evidence to consider σ_1R antagonists as an innovative and alternative approach for treating pain, especially neuropathic pain but also other sensitizing pain conditions. In addition, preclinical evidence has pointed out their potential as an adjuvant therapy to enhance opioid analgesia, without increasing the side effects associated with opioid use [11, 21–23]. As an advantage over opioids, σ_1R antagonists do not alter normal basic pain behavior as they do not modify the normal sensory mechanical and thermal perception in the absence of sensitizing stimuli. That is, σ_1R antagonists exert antiallodynic and antihyperalgesic effects in sensitizing conditions, enabling the reversal of diminished nociceptive thresholds back to normal values, but they do not modify normal sensory thresholds in non-sensitizing conditions, i.e., in normal conditions, in the absence of injury or other inductors of pain hypersensitivity [13, 24–26]. The σ_1R, however, modulates opioid-mediated antinociception in acute non-sensitizing models. σ_1R agonists diminish opioid antinociception whereas antagonists enhance it [21, 27, 28]. As an example, the σ_1R antagonist E-52862 was devoid of activity in the radiant heat tail-flick test but it did potentiate by a factor of 2–3.3 the antinociceptive effect of several opioids, including tramadol, morphine, buprenorphine, codeine, oxycodone, and fentanyl in this acute test. Moreover, E-52862 was effective in restoring antinociception of morphine once tolerance had developed [22].

The purpose of this review is to summarize the current knowledge on the potential of a new drug class, σ_1R antagonists, for the treatment of pain of different etiologies (e.g. neuropathic, inflammatory, visceral, orofacial, postoperative), either used alone or in combination with known analgesics such as opioids**.** Evidence was gained experimentally using genetic approaches, i.e. by the use of σ_1R KO mice or antisense probes, pharmacological tools, experimental drugs in discovery and clinical development phases as well as non-selective marketed drugs. Due to the chaperoning activity of the σ_1R, we have also summarized the current understanding of its interaction with different other molecular targets involved in pain transduction, transmission and processing, to provide some mechanistic background to the observed antinociceptive effects of σ_1R antagonists.

8.2 σ_1R Modulation of Pain Targets

The σ_1R, as a ligand-operated chaperone, is able to interact with other proteins including receptors, enzymes or ion channels, some of which are involved in nociception. Pain is a complex pathology, involving several mechanisms engaging many different molecular targets and intracellular pathways either at central or peripheral nervous system (PNS) [29]. Provided that the σ_1R may act as a chaperone for several of those targets, it can regulate pain at different levels. Here we summarize current knowledge on σ_1R molecular partners in nociception.

8.2.1 Ion Channels

8.2.1.1 Voltage-Gated Sodium Channels

Nociceptors detect noxious stimuli and transmit this sensation to the CNS by means of action potentials, whose generation involves fast inward sodium currents [30]. A direct interaction of σ_1R with neuronal sodium channels has not been described yet, but a physical interaction with the cardiac $Na_v1.5$ has been reported [31]. Both the non-selective σ_1R antagonist haloperidol and the σ_1R agonist (+)-pentazocine have been described to disrupt the $Na_v1.5/\sigma_1$R interaction, haloperidol being more efficacious in reducing this interaction [31]. Accordingly, independent on the agonistic or antagonistic nature of ligands, σ_1R agonists [(+)-SKF-10047 and (+)-pentazocine] and non-selective σ_1R/σ_2R ligands including haloperidol (antagonist) and 1,3-di-o-tolyl-guanidine (DTG) (agonist) all reversibly inhibited

$Na_v1.5$ channels to varying degrees in HEK-293, COS-7 cells and neonatal mouse cardiac myocytes [32]. Patch-clamp recordings in HEK293 cells stably expressing the human cardiac $Na_v1.5$ also revealed inhibitory modulation by some σR ligands, such as (+)-SKF-10047 and dimethyltryptamine (DMT), which was reverted by progesterone to varying degrees, consistent with antagonism of σ_1 and/or σ_2 receptors, and in some cases by σ_1R knockdown with small interfering RNA [33]. Similarly, patch-clamp experiments in isolated intracardiac neurons from neonatal rats revealed that the non-selective σ_1R/σ_2R agonist DTG and the σ_1R selective agonist (+)-pentazocine inhibited voltage-gated sodium channels. The selective σ_1R antagonist BD-1063 did not modulate the current but inhibited DTG block of sodium currents by ~50 %, suggesting that the effects involve, at least in part, σ_1Rs [34]. It is also worth to mention that activation of σ_1R modulates persistent sodium currents in rat medial prefrontral cortex [35], which are a part of the sodium current involved in setting the membrane resting potential in a subthreshold range and hence regulate repetitive firing and enhance synaptic transmission [36]. It has been described that human $Na_v1.8$ channel, a tetrodotoxin-resistant voltage-gated sodium channel expressed by DRGs with a strong implication in pain modulation, displays slower inactivation kinetics and a larger persistent current than already described for this channel in other species [37]. It is tempting to speculate that the interaction of σ_1R described for the $Na_v1.5$ could as well apply for other sodium channels involved in pain, such as $Na_v1.8$ channels, and that its regulation of persistent sodium current in neuronal areas involved in pain could explain part of its role in nociception. Nevertheless, studies investigating the relationship between σ_1R and sodium channels have been hampered by the lack of selectivity of several of the pharmacological tools utilized, thus precluding generalized conclusions. As an example, σ_1R agonists such as (+)-SKF-10047, dextromethorphan and DTG have been found to directly inhibit $Na_v1.2$ and $Na_v1.4$ currents, apparently through a σ_1R-independent mechanism [38].

8.2.1.2 Acid-Sensing Ion Channels

Acid-sensing ion channels (ASICs) are cationic (sodium-permeable) channels activated by extracellular protons, which are responsible for acid-evoked currents in neurons. They are involved in nociception but also in learning, memory and in pathological conditions such as ischemic stroke [39]. A direct interaction between σ_1R and ASIC has been described, which can be modulated by σ_1R ligands. The σ_1R antagonist haloperidol was able to reduce the ASIC1a/σ_1R binding about 50 % [40]. Moreover, σ_1R/ASIC physical interaction has also functional consequences. σ_1R agonists decreased acid-induced ASIC1a currents and intracellular calcium elevations in rat cortical neurons [41], an effect ascribed to σ_1R engagement because the inhibitory effect was counteracted using σ_1R antagonists. In contrast, in ischemic pain induced by hindlimb thrombus, the σ_1R antagonist BD-1047 reduced mechanical allodynia at the periphery synergistically with the ASICs blocker amiloride, whereas the σ_1R agonist PRE-084 induced mechanical allodynia when co-administered with an acidic pH solution, thus suggesting that σ_1R activation facilitates ASICs to promote pain [42].

8.2.1.3 Voltage-Gated Potassium Channels

Potassium channels are also very important players in action potentials driving repolarization. When these channels open, potassium ions cross the membrane to limit neuronal excitability and firing rate. Potassium channels have also been involved in pain [43]. Specific $K_v1.2$ antibodies were shown to co-immunoprecitate the σ_1R in the nucleus accumbens medial shell [44]. This interaction was further confirmed in double transfected NG108–15 cells. $K_v1.2$ is a delayed rectifier channel activated by slight membrane depolarization. In the PNS, $K_v1.2$ are found in the soma and juxtaparanodes of medium-large DRG neurons and are largely decreased after axotomy, which may contribute to the hyperexcitable phenotype (mechanical and cold allodynia) observed after such type of injury [43]. Aydar and colleagues also demonstrated a direct inter-

action of σ_1R with the K_v1.4 in transfected xenopus oocytes and in rat posterior pituitary tissue [45]. σ_1R agonists could elicit a decrease in K_v1.4 conductance in double transfected oocytes, but the co-expression of σ_1R with K_v1.4 resulted in a faster rate of channel inactivation, a reduction in net current efflux and no change in the channel voltage-dependence activation. This ligand independent regulation and the physical interaction with K_v1.4 made Kourrich and colleagues suggest σ_1Rs as auxiliary subunits for voltage-activated potassium channels [44]. An important observation is that K_v1.4 channels are the only K_v1 α subtype expressed in small diameter DRG neurons, meaning that this channel subtype is in charge of potassium conductance in Aδ and C nociceptor fibers [46]. The regulation of this subtype of potassium channel by σ_1R in this particular type of nociceptors is consistent with the regulatory role that σ_1R plays in pain modulation.

8.2.1.4 Calcium-Activated Potassium Channels

Apart from voltage-sensitive potassium channels, σ_1R has been described to regulate non voltage-dependent, small conductance (SK) calcium-activated potassium channels [47]. SK channels activation, secondary to calcium increases after action potentials, produces membrane hyperpolarization to reduce firing frequency of repetitive action potentials [48]. Ca^{2+} entry after synaptic activation opens SK channels that act to limit the amplitude of synaptic potentials and reduce Ca^{2+} influx through the *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) [49]. It has also been established that Ca^{2+} influx through NMDAR could open Ca^{2+}-activated K^+ channels in several systems. Using the σ_1R agonist (+)-pentazocine and patch-clamp whole-cell recordings in CA1 pyramidal cells of rat hippocampus, potentiation of NMDAR-mediated responses was found to occur via inhibition of SK channels, that would normally reduce the amplitude of synaptic potentials reducing Ca^{2+} influx through NMDARs [47]. Moreover, the enhanced NMDAR activity was translated into an increased synaptic plasticity as evidenced by a long-term potentiation effect [47]. Another study also found that DTG inhibited SK channel in midbrain dopaminergic neurons and transiently transfected HEK-293 cells, but other σ_1R agonists such as carbetapentane, (+)-SKF-10047 and PRE-084 had no or little effect. The effect of DTG was not affected by high concentrations of the σ_1R antagonist BD-1047, which argue against a coupling of σ_1Rs to SK channels and suggests that DTG directly blocks SK channels [50]. In the absence of further studies it is difficult to know whether σ_1R actually regulates NMDAR via SK channels or it is a ligand- or cell type-dependent finding.

8.2.1.5 Voltage-Gated Calcium Channels

Voltage-gated calcium channels (VGCC) are other ion channels involved in neuronal action potential that contribute to pain pathophysiology [51]. Tchedre and colleagues, based on co-immunoprecipitation studies, proposed the interaction between the σ_1R and the L-type VGCC endogenously expressed in the RGC-5 retinal ganglion cell line [52]. At the functional level, they found that the σ_1R agonist (+)-SKF-10047 inhibited potassium chloride-induced calcium influx in the RGC-5 cell line and calcium currents in rat cultured primary RGCs [52]. Also in retinal ganglion cells, co-localization studies demonstrated that σ_1Rs and L-type VGCCs co-localized and calcium imaging studies showed that σ_1R agonists (+)-SKF10047 and (+)-pentazocine inhibited calcium ion influx through activated VGCCs (L-type). Antagonist treatment using BD-1047 potentiated Ca^{2+} influx through activated VGCCs and abolished inhibitory effects of the σ_1R agonists [53]. Data obtained using rat intracardiac and superior cervical ganglia neurons also revealed that σ_1R ligands decreased calcium channel currents with maximum inhibition ≥95 %, suggesting that σ_1Rs act on all calcium channel subtypes found on the cell body of these sympathetic and parasympathetic neurons, which includes N-, L-, P/Q-, and R-type calcium channels [54]. In addition to affecting a broad population of calcium channel types, σ_1R ligands altered the biophysical properties of these channels (channel inactivation rate was accelerated, and the voltage dependence of both steady-state

inactivation and activation shifted toward more negative potentials). Interestingly, both σ_1R agonists and antagonists depressed calcium channel currents, with a rank order of potency (haloperidol > ibogaine > (+)-pentazocine > DTG) consistent with the effects being mediated by σ_2R and not by σ_1R [54]. Most interestingly, a similar behavior has been described in dissociated rat DRG neurons, as σ_1R agonists (+)-pentazocine and DTG inhibited calcium currents in patch-clamp experiments [55]. The effect was ascribed to σ_1R activation as it was blocked by the σ_1R antagonists BD-1063 or BD-1047. Both (+)-pentazocine and DTG showed similar inhibitory effect on axotomized DRG neurons as they shifted the voltage-dependent activation and steady-state inactivation of VGCC to the left and accelerated VGCC inactivation rate in both control and axotomized DRG neurons. On the contrary, while the antagonist BD-1063 had no effect by itself in normal non-injured DRGs, its application increased calcium currents in the axotomized ones. Pan and colleagues already noticed these paradoxical results, as σ_1R antagonists exert antinociceptive effects while σ_1R agonists are pronociceptive, and it is also known that painful nerve injury is accompanied by reduction of calcium current in axotomized sensory neurons, which in turn results in elevated sensory neuron excitability [55]. Similarly, it should be noted that calcium current inhibition by compounds such as gabapentin or pregabalin is also an antinociceptive strategy. The complexity and heterogeneity of calcium channel signaling throughout neuronal regions involved in pain was argued in order to explain this apparent contradiction. While at the dorsal horn terminals calcium channel activity controls neurotransmitter release and its blockade results in less neurotransmission and hence pain relief, calcium channel inhibition elsewhere (and particularly at the periphery) can result in inhibition of calcium-activated potassium channels that are in control of after-hyperpolarization, membrane excitability, and firing frequency, leading to an opposite final output. That is, lowered inward calcium current has the dominant, overriding effect of decreasing outward current through calcium-activated potassium channels, thus reducing after-hyperpolarization and thereby increasing excitability. Antagonism of sensory neuron σ_1Rs at peripheral sites (including DRGs) may thus relieve pain by rescuing calcium currents required for natural suppression of repetitive firing via opening of calcium-activated potassium channels.

8.2.1.6 Ligand-Gated Calcium Channels

Ligand-gated calcium channels such as glutamate NMDARs also interact with σ_1R. Increased calcium influx through NMDAR and increased level of phosphorylation of these glutamate receptors have been reported following the activation of σ_1R [25, 56, 57]. This increase in the NMDAR phosphorylation state and activity is accompanied by enhanced pain behaviors. Very recently, a direct physical interaction of the σ_1R with the C-terminal of the NMDAR NR1 subunit has been described [58–60] both *in vitro* an *in vivo* using different research approaches. This physical interaction also modulates the cross-talk between opioid analgesia and NMDAR activity [61, 62]. σ_1R activation is pronociceptive, increasing NMDAR activity as explained above. Garzon's group has shown how σ_1R antagonists are able to uncouple the σ_1R-NMDAR association while increasing opioid analgesia and reducing the development of opioid tolerance (Fig. 8.1). All these evidence suggest a role of the σ_1R in the regulation of synaptic plasticity, as NMDAR has been described to mediate different forms of plasticity including long-term potentiation and central sensitization, phenomena linked to forms of pain facilitation such as hyperalgesia and allodynia [63, 64].

8.2.2 G Protein-Coupled Receptors (GPCRs) and Intracellular Second Messenger Machinery

Several G protein-coupled receptors, including targets clearly involved in pain such as the cannabinoid CB_1 and μ-opioid (MOR) receptors [65, 66] have been described as σ_1R partners. Opioids are still the most used analgesics in severe pain

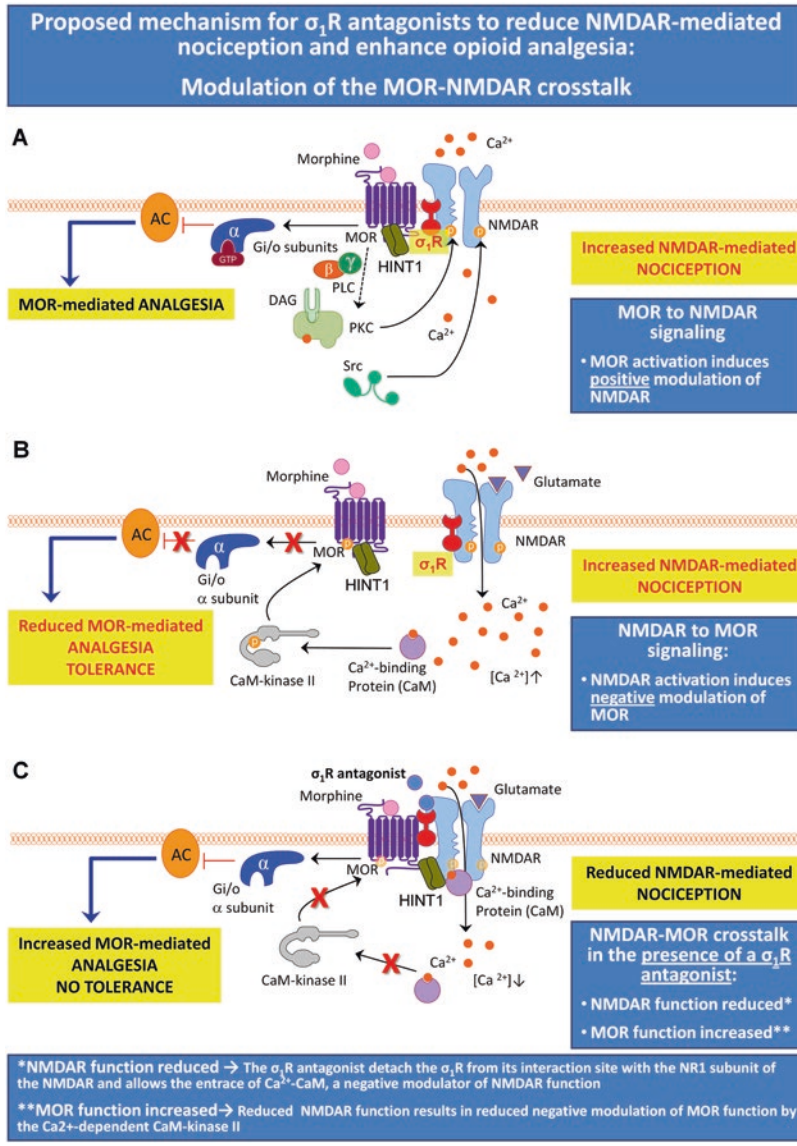

Fig. 8.1 Proposed mechanism for σ_1R antagonists to enhance opioid analgesia based on recent studies reporting modulation of the MOR-NMDAR crosstalk by σ_1R (Rodríguez-Muñoz et al., Antioxidants & Redox Signaling, 2015). σ_1R associates in a calcium-dependent manner with NMDAR NR1 subunits and modulates NMDAR-mediated signaling. Because the σ_1R also associates with the MOR, this protein regulates opioid function within a protein assembly that, via the HINT1 protein, supports MOR-NMDAR physical association and functional cross-regulation. (Panel **a**): MOR to NMDAR signaling: MOR activation induces positive modulation of NMDAR. Upon MOR activation, NMDARs are phosphorylated, increasing their activity and thus NMDAR-mediated nociception. (Panel **b**): NMDAR to MOR signaling: NMDAR activation induces negative modulation of MOR. As a consequence of increased calcium influx through NMDARs, the calcium-calmodulin dependent kinase II becomes activated and phosphorylates MORs, which reduces MOR-mediated analgesia and the response to subsequent morphine challenges (promotes tolerance). (Panel **c**): NMDAR-MOR crosstalk in the presence of a σ_1R antagonist. The absence of σ_1R (e.g. in KO animals) or treatment with a σ_1R antagonist to detach σ_1R from the NMDA NR1 subunit allows the entrance of negative regulators of NMDARs, likely calcium-calmodulin, thus reducing NMDAR function and impairing its negative feedback on MORs. Accordingly, it is proposed that a mechanism by which σ_1R antagonists enhance opioid analgesia is by releasing MORs from the negative influence of NMDARs

conditions [67]. σ_1R modulation of opioid receptors was initially described by Chien and Pasternak [21, 27] demonstrating that σ_1R antagonists potentiate opioid analgesia. At the *in vitro* level, Kim and colleagues demonstrated both a physical, by co-immunoprecipitation experiments, and a functional interaction between MOR and σ_1R in transfected HEK cells. The functional consequences of such an interaction were assessed by means of a GTPγS assay, antagonists increasing opioid efficacy by shifting the EC_{50} values of opioid-induced GTPγS binding by 3- to 10-fold to the left [66]. Cannabinoid receptors also play a role in analgesia and they have been shown to be distributed both in peripheral and CNS regions important for pain transmission [68]. Similarly to MOR, a physical interaction with σ_1R has been described for CB_1 receptors [65]. A functional *in vivo* relationship between these two receptors was demonstrated using the tail-flick test. The NMDAR increased its activity in σ_1R KO mice and it was no longer regulated by cannabinoids as in wild-type (WT) counterparts. Moreover, NMDAR antagonism in the σ_1R KO animals produced no effect on cannabinoid analgesia. Pharmacological intervention showed similar results, because antagonizing σ_1R prevented NMDAR antagonists from reducing CB1 receptor-induced analgesia. For both σ_1R-MOR-NMDAR and σ_1R-CB_1-NMDAR protein complexes, histidine triad nucleotide binding protein 1 (HINT1) has been shown to be another interacting partner. Inhibitors of HINT1 enzymatic activity have been described to enhance morphine-induced analgesia while reducing the development of opioid tolerance [69]. A direct physical interaction between this protein and the σ_1R has been shown recently [65] and the coordinated interaction of HINT1 and σ_1R with NMDAR and its GPCRs partners is able to control the analgesia mediated through those GPCRs (Fig. 8.1). Nociceptors are activated by diverse mediators, such as glutamate, bradykinin, and substance P, which act through GPCRs coupled to Gαq proteins. These Gαq proteins lead to the activation of the phospholipase C (PLC) cascade of intracellular second messengers leading to the release of Ca^{2+} from intracellular stores [70]. The ability of σ_1R to modulate this pathway, and so indirectly GPCRs coupled to the PLC-inositol triphosphate (IP_3)-calcium signaling cascade, represents another link to pain modulation. σ_1R activation has been also shown to stimulate PLC to produce diacylglycerol (DAG) and IP_3 [71] which in turn leads to the activation of IP_3 receptors and efflux of calcium to the cytoplasm. There is growing evidence that σ_1R is an important player at the endoplasmic reticulum (ER) regulating calcium homeostasis. In such a role, σ_1R interacts directly with ankyrin B, BiP or IP_3 receptors [72–74] and ultimately regulates intracellular calcium mobilization from the ER either to the cytosol or to mitochondria in the mitochondria-associated ER membrane (MAM) [74]. σ_1R activation leads to a diminished interaction with ankyrin and BiP, an increase in its interaction with IP_3 receptor and finally a stabilization of this later one facilitating calcium efflux. σ_1R agonists also caused the dissociation of ankyrin B and IP_3 receptors and this activity correlated with the ability of these ligands to potentiate intracellular mobilization induced by bradykinin. This increase in calcium could be reversed by a σ_1R antagonist [75]. Similarly, in CHO cells overexpressing a C-terminal EYFP tagged σ_1R, agonists, such as (+)-pentazocine and PRE-084, caused significant uncoupling of the σ_1R-BiP complex, whereas antagonists, such as NE-100 or haloperidol, were not able to modify that complex at all [73].

8.2.3 Homomerization

Finally, σ_1R interacts with itself [76, 77]. A GXXXG motif of the σ_1R is involved in the oligomerization process, as mutations of this σ_1R region reduced the number of receptors in higher oligomeric states and favored smaller oligomeric ones [78]. Moreover, only oligomeric and not the monomeric forms of σ_1R could bind the specific agonist (+)-pentazocine. Another finding by Gromek and colleagues was that ligand binding to σ_1R oligomers could prevent the formation of the monomer form, emphasizing the important role that σ_1R oligomers have on its pharmacology [78].

Thus, pharmacological activity of σ_1R ligands, including their pro- or antinociceptive activities, could be at least in part consequence of their influence in regulating and/or interacting with σ_1R oligomeric states.

8.3 Sigma-1 Receptor Antagonism as a New Analgesic Strategy

8.3.1 Synthetic Sigma-1 Receptor Antagonists

Many structurally diverse compounds bind to the σ_1R (agonists, Fig. 8.2 and antagonists, Fig. 8.3). Several compounds have undergone clinical trials, but only E-52862 is being developed for pain indications. In fact, no selective σ_1R ligands have so far been marketed, although many drugs on the market show affinity for the σ_1R [20].

While a long list of xenobiotic compounds interact with the σ_1R, there are few known endogenous small molecules showing binding affinity to the receptor. Endogenous compounds that have been proposed as putative endogenous σ_1R ligands include neurosteroids, some sphingolipids and dimethyltryptamine (Figs. 8.2 and 8.3). Their exact physiological roles in the context of the modulation of σRs are still not clear, but it is remarkable that none of them show high affinity for the σ_1R and only one, progesterone, is described as a σ_1R antagonist.

Clinically used drugs with an affinity for the σ_1R include drugs with different therapeutic applications, such as antipsychotics (haloperidol: D2/D3 antagonist), antidepressants (fluvoxamine, sertraline, fluoxetine, imipramine: SSRI

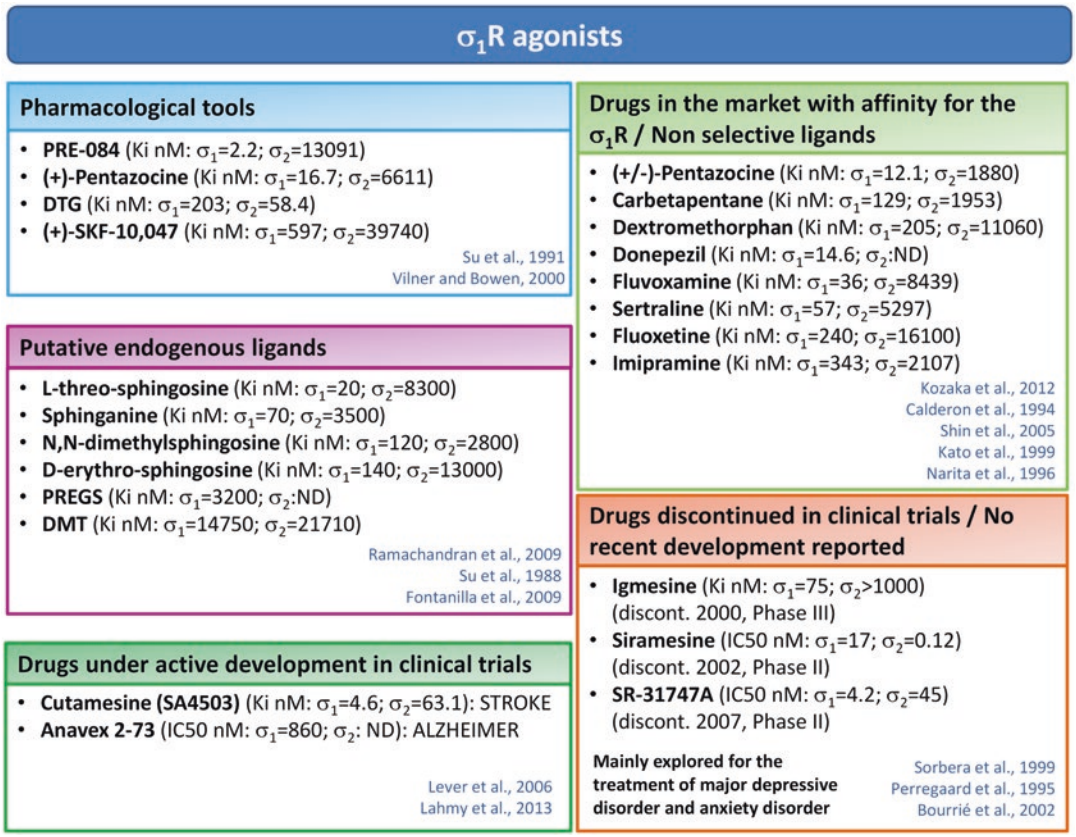

Fig. 8.2 σ_1R agonists

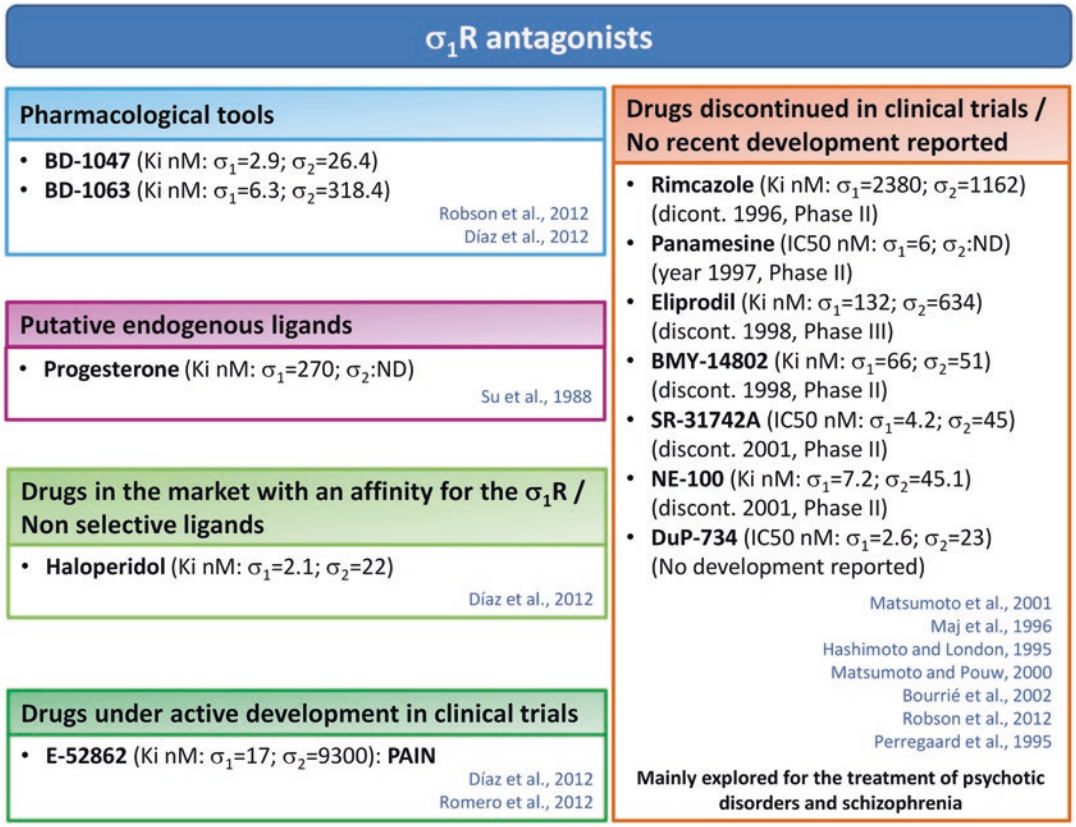

Fig. 8.3 σ_1R antagonists

and non-SSRI), analgesics (pentazocine: opioid agonist), antitussives (carbetapentane: muscarinic antagonist, dextromethorphan: NMDA antagonist) and drugs for the treatment of neurodegenerative disorders such as Alzheimer's disease (donepezil: cholinesterase inhibitor). All of these drugs can bind to σ_1R with high to moderate/weak affinity, but none of them show selectivity over other main therapeutic targets. Haloperidol acts as a σ_1R antagonist, whereas fluvoxamine, sertraline, fluoxetine, imipramine, pentazocine, carbetapentane, dextromethorphan and donepezil act as σ_1R agonists (see [6] for a review). In spite of their lack of selectivity, several of these compounds have been used as pharmacological tools in understanding the role of the σ_1R in pain. Details on their activities in different pain models can be found in [6] and are also briefly described in the following sections.

Since the mammalian and human σ_1Rs were cloned in 1996 [79, 80], new high affinity ligands for the σ_1R have been developed. In the 1990s and in early 2000s some σR ligands reached Phase II clinical trials for the treatment of neuropsychiatric disorders, but most of them did not progress up to Phase III. No information on their clinical use in pain is available. Proposed σ_1R agonists discontinued in clinical development (Fig. 8.2) include: igmesine (Phase III; depression and Alzheimer's disease; Pfizer Inc.), siramesine (Phase II; anxiety disorder; H Lundbeck A/S and Forest Laboratories Inc.), SR-31747A (Phase II; rheumatoid arthritis and cancer; Sanofi-Synthelabo). Proposed σ_1R antagonists discontinued in clinical development (Fig. 8.3) include: rimcazole (Phase II; psychotic disorder; GlaxoSmithKline), panamesine (Phase II; psychotic disorder and schizophrenia; Merck KGaA),

eliprodil (Phase III; head injury and stroke, Synthelabo and Lorex Pharmaceuticals Inc), BMY-14802 or BMS-181100 (Phase II; psychotic disorder and schizophrenia; Bristol-Myers Squibb Co), SR-31742A (Phase II; psychotic disorder and schizophrenia; Sanofi-Synthelabo), NE-100 (Phase II; psychotic disorder and schizophrenia; Taisho Pharmaceutical Co Ltd) and DuP-734 (No development reported; psychotic disorder and schizophrenia; Bristol-Myers Squibb Pharma Co). As recently reviewed [6, 20], these compounds were defined as σ_1R ligands, but information on both the molecular structure of the σ_1R and structural, functional-determining features of σ_1R ligands was very poor at that time. Many of them were not selective versus σ_2R and/or other molecular targets. In addition, a number of them showed suboptimal metabolic profiles or were highly lipophilic, reasons that may have affected their potential development. Thus, past clinical failures do not preclude a potential role of σ_1R modulation in the above cited indications.

Only recently, more selective and optimized compounds have become available for the accurate assessment of the σ_1R as a therapeutic target. Since 2006, some σ_1R ligands have been extensively studied for their potential in treating both acute and chronic neurodegenerative diseases and neuropathic pain. σR ligands commercially available and used as pharmacological tools include PRE-084, (+)-pentazocine, DTG and (+)-SKF-10,047 as agonists (Fig. 8.2); and BD-1047, BD-1063 and NE-100 as antagonists (Fig. 8.3). Although they have been very useful to ascertain the role of the σ_1R in pain, some of them are still not selective enough to draw definitive conclusions, and sometimes paradoxical or inconsistent results have been reported. Details on their activities in different pain models can be found in [6, 20], and are also briefly described next in this chapter.

To date, three pharmaceutical companies, Anavex Life Sciences Corp. (with the σ_1R agonist Anavex 2–73), M's Science Corp. (with the σ_1R agonist cutamesine) and ESTEVE (with the σ_1R antagonist E-52862 or S1RA) are actively engaged in clinical trials of σ_1R ligands. The R&D team of ESTEVE disclosed a wide series of compounds with affinity for the σ_1R, selecting E-52862 for clinical development. E-52862 has been a very useful tool to assess the role of the σ_1R in pain, as it shows high affinity for the σ_1R (Ki = 17 nM) and has high selectivity over the σ_2R and many other molecular targets [26]. In the recent years, E-52862 (many times identified as S1RA) has been used to explore the potential of σ_1R antagonists in pain indications of different etiology, as well as in understanding the mode of action of this new class of drugs [11, 15, 18, 19, 21–23, 26, 81–83]. The safety and pharmacokinetic profile of E-52862 were studied in a rigorous Phase I program, showing favorable safety results at all doses tested [84, 85]. Today, the E-52862 clinical program focuses on pain management as opioid-adjuvant therapy and as monotherapy in several neuropathic pain conditions, including diabetic-, post-operative-, and chemotherapy-induced neuropathic pain.

8.3.2 Sigma-1 Receptor Modulation of Opioid Analgesia

Opioids are the gold standard painkillers used for the treatment of moderate to severe pain. Although they are used worldwide, they exert well-known side effects that limit their use such as constipation, dizziness and nausea, among others, which usually lead to treatment discontinuation [86]. Other side effects, such as tolerance and dependence appear in long-term treatments. Consequently a reduction in treatment effectiveness and increase consumption are normally associated with opioids use, increasing the risk of death from multiple causes compared with non-users [87]. Thus, in order to minimize opioid-related adverse events, several approaches combining other drugs with opioids to increase their potency and consequently reduce the opioid doses, have been proposed.

A relationship between the σR system and opioid analgesia was described more than 20 years ago by Chien and Pasternak. They showed that σ_1R agonists counteracted opioid receptor-mediated analgesia, while σ_1R antagonists

potentiated it [21, 24, 27, 88]. The systemic administration of (+)-pentazocine or DTG (σ_1R agonists) inhibited whereas haloperidol (D2 receptor and σ_1R antagonist) enhanced morphine antinociception in the tail-flick test in mice and rats [21, 24]. The enhancing effect of haloperidol was mediated by σ_1R blocking, since (−)-sulpiride (selective D2 receptor antagonist) was unable to potentiate opioid analgesia [21, 27]. The actions of σ_1R ligands were not limited to the modulation of morphine analgesia. Treatment with σ_1R receptor ligands modulates the antinociception induced by other μ-, δ and κ-opioid receptor agonists, such as D-penicillamine-2-D-penicillamine-5-enkephaline, U-50488H, nalbuphine or naloxone benzoylhydrazone [21, 24, 28, 89, 90]. The modulation of opioid analgesia by σ_1R ligands was later supported by studies using other σ_1R agonists ([+/−]-PPCC) and antagonists ([+]-MR200, compound 9, BD-1063 or E-52862) [22, 90–93] as well as σ_1R antisense oligodeoxynucleotides [28, 89, 94, 95].

Altogether, data support the presence of an endogenous σ_1R system, tonically active, whereby σ_1R exerts a tonic inhibitory control on the opioid receptor-mediated signaling pathways. This endogenous system can be pharmacologically counteracted by using σ_1R antagonists to increase the response to opioids. This pharmacological interaction has been supported by molecular studies, already described in this review (see σ_1R modulation of pain targets section and Fig. 8.1). σ_1R antagonists enhance opioid analgesia in naïve mice by releasing MORs from the negative influence of NMDARs, and even more, they also reset antinociception in morphine-tolerant animals [60], which support a previous result with systemically administered drugs where the σ_1R antagonist E-52862 restored morphine-induced antinociception in morphine tolerant mice [22].

Regarding the site of action, the modulation of opioid-induced antinociception has been observed both at peripheral and central (mainly supraspinal) levels, suggesting that σ_1R-mediated pain modulation occurs at different sites [11, 22, 23]. The supraspinal site of action of σ_1R was firstly demonstrated by the use of the σ_1R agonist (+)-pentazocine microinjected in periaqueductal gray, locus coeruleus, or RVM. It diminished systemic opioid analgesia in the tail-flick model in mice. In turn, the σ_1R antagonist haloperidol and also antisense oligonucleotides microinjected into the RVM markedly enhanced the analgesic actions of co-administered morphine. On the contrary, σ_1R agonists spinally administered did not alter opioid analgesia [28, 95].

A peripheral site of action of σ_1R in the modulation of opioid-induced antinociception has been recently reported by using the paw pressure test in mice [11, 23]. BD-1063, BD-1047, NE-100 and E-52862 were devoid of effect in mechanical nociception when administered locally (intraplantarly). However, these σ_1R antagonists markedly potentiated opioid antinociception of an inactive dose of morphine, their effects being reversed by the selective σ_1R agonist PRE-084 [23]. In addition, σ_1R KO mice exhibited an enhanced mechanical antinociception in response to morphine (local or systemic) [23]. Similar findings were observed using other opioids such as fentanyl, oxycodone, buprenorphine, tramadol or even the peripheral opioid loperamide [11]. The peripheral component of the enhancement of opioid antinociception by σ_1R antagonists was also evidenced by using the radiant heat tail-flick test in rats [96]. In this study, the systemic administration of peripheral opioid agonist loperamide was devoid of antinociceptive effect when given alone but produced antinociception when combined with E-52862. Accordingly, the antinociceptive effect of the combination was abolished by the systemic administration of the peripheral opioid antagonist naloxone methiodide.

It is worthwhile that the increase in opioid potency by σ_1R antagonists co-administration appears to be limited to analgesia and not to side effects. E-52862 enhanced by a factor of 2–3.3 the antinociceptive effect of several opioids in the tail-flick test, including tramadol, morphine, buprenorphine, codeine, oxycodone, and fentanyl. The antinociceptive effect was attributed to the σ_1R, provided that E-52862 was devoid of potentiation effect on morphine analgesia in mice lacking σ_1R. However, morphine-induced antinociceptive tolerance and rewarding were attenuated whereas physical dependence, inhibition of

gastrointestinal transit, or mydriasis were not modified [22]. Finally, in addition to opioid analgesia, the σ_1R antagonist BD-1047 has been shown to potentiate clonidine analgesia without affecting the motor impairment produced by the alpha-2 adrenoceptor agonist in the mouse orofacial formalin model [97], thus suggesting the possibility that the σ_1R system could be modulating other antinociceptive systems different from opioids.

In summary, σ_1R antagonists have been shown to systemically and peripherally potentiate opioid analgesia but not opioid-related adverse effects, which suggest an application for σ_1R antagonists as opioid adjuvant therapy.

8.3.3 Sigma-1 Receptor Antagonists for the Treatment of Neuropathic Pain

Neuropathic pain has been defined by the IASP (International Association for the Study of Pain) as "Pain caused by a lesion or disease of the somatosensory nervous system, either peripheral or central". This type of pain is chronic and can be extremely severe and crippling for the individual. Neuropathic pain is described by patients as a persistent, diffuse, burning-like sensation with no specific location in a given organ or tissue. In addition, they suffer from paroxysmal pain, that is, short electric shock-like sensations alternating with remission periods. Neuropathic pain is one of the most challenging types of pain because effective and safe neuropathic pain treatment remains a largely unmet therapeutic need [98]. Neuropathic pain patients show general insensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and relative resistance to opioids. Moreover, some of these drugs involve dose limitations with respect to efficacy and side effects.

Studies using σ_1R KO mice and new selective σ_1R antagonists have identified the σ_1R as a key participant in the modulation of pain behavior in sensitizing and chronic pain conditions, supporting the use of the selective σ_1R antagonists for the treatment of neuropathic pain [93]. σ_1R KO mice are a useful genetic tool to study the involvement of σ_1R in several pain types, provided that KO mice perceive and respond normally to stimuli of different nature (mechanical, chemical and thermal). Thus, the absence of σ_1R in KO mice has been shown to not interfere with the perception of several stimuli applied to the hind paw or with the motor response required for paw withdrawal [12, 14–16, 26]. In σ_1R KO mice, both phases of formalin-induced pain were clearly reduced [12] and capsaicin injected intraplantarly did not induce mechanical allodynia [13]. Regarding neuropathic pain models, cold and mechanical hypersensitivity were strongly attenuated in σ_1R KO mice treated with paclitaxel (concomitant with paclitaxel-induced sensory nerve mitochondrial abnormalities) [15] or exposed to partial sciatic nerve ligation (PSNL) [14], supporting a role of this receptor in the development of the neuropathic pain.

σ_1R antagonists administered alone fail to modify pain by themselves in classical models of thermal and mechanical acute nociception, as seen in the tail-flick, the hot plate and the paw pressure tests in rodents [14, 23, 92]. However, when σ_1R antagonists are administered in sensitizing and chronic pain models they produce similar results as those described in the σ_1R KO mice. The σ_1R antagonist haloperidol, its metabolites I and II and E-52862 inhibited formalin-induced pain [26, 99] and capsaicin-induced sensitization in mice [26, 100]. Pain-related behaviors have also been reversed using σ_1R antagonists in neuropathic pain models in mice, such as the chronic compression of the DRG [101], PSNL [26] and paclitaxel-induced neuropathic pain [15], among others. In an operant self-administration model, mice with PSNL, but not sham-operated animals, self-administered E-52862. In addition, an anhedonic state (decrease in the preference for 2 % sucrose solution) was revealed in nerve-injured mice, which was attenuated by E-52862. Thus, it was concluded that E-52862 showed antinociceptive efficacy following nerve injury associated with an improvement of the emotional negative state

and was devoid of reinforcing effects [82]. Paradoxically, some studies have reported antinociceptive activities in neuropathic pain related to σ_1R agonist activity [102, 103]. The σ_1R agonist (+)-pentazocine acutely injected into the dorsal surface of the hindpaw produced an antinociceptive effect on mechanical allodynia induced in streptozotocin-induced diabetic mice. The effect was inhibited by local hindpaw pretreatment with the σ_1R receptor antagonist BD-1047 in the same area [102]. The authors suggested that the antinociceptive effect of (+)-pentazocine involves lowering of nitric oxide (NO) metabolites in the hindpaw and was discussed as a possible dose effect (peripheral application of the σ_1R agonist (+)-pentazocine could produce the nociceptive response at lower dose, whereas, at higher doses as used in the study, it produces the antiallodynic effect). Attenuation of calcium channel currents involved in peripheral nerve transmission was also discussed as a possible underlying mechanism for the antiallodynic, local, peripheral effect of (+)-pentazocine. In this sense, the σ_1R agonist SA-4503, but not the σ_1R antagonist NE-100, was found to produce antinociceptive effects against chemotherapeutic-induced neuropathic pain in rats [103]. The reasons for these apparent discrepancies are not clear, but the categorization of σ_1R ligands as agonists or antagonists is still unclear and several factors, including drug concentration, site of application, readouts, and diverse experimental conditions could account for these differences.

Several studies have reported changes in σ_1R expression in some phases of the experimental neuropathic models, further supporting the involvement of the σ_1R in the development of the neuropathic pain. σ_1R expression is up-regulated in the spinal cord during the induction phase of neuropathic pain following sciatic nerve constriction or chronic compression of the DRG [57, 101, 104] and in the brain 10 weeks after the induction of diabetic neuropathy [105]. However, the expression of σ_1R was reduced in the spinal cord following chemotherapy (oxaliplatin and paclitaxel) treatment [103] and in DRGs following spinal nerve ligation [10]. Thus, a general rule on how σ_1R expression is modified in neuropathic pain conditions cannot be established.

σ_1R has been involved in the activation of the extracellular signal-regulated kinase (ERK) in the spinal cord in neuropathic pain models such as chronic constriction compression of the DRG, PSNL, and paclitaxel-induced neuropathic pain [14, 15, 101]. In particular, ERK phosphorylation within the spinal cord has been associated with mechanical and cold allodynia in animal models of neuropathic pain. Accordingly, σ_1R KO mice, that exhibited reduced cold allodynia and did not develop mechanical allodynia as compared to WT mice, showed reduced ERK phosphorylation in the spinal cord [14, 15].

ERK activation feeds back on the NMDAR by increasing the expression and phosphorylation status of its NR1 subunit, leading to NMDAR over-activation during neuropathy. It is known that the σ_1R plays an important role in modulating NMDA activity because: (i) pain-related NR1 phosphorylation and expression increase are enhanced by σ_1R agonists and blocked by σ_1R antagonists [25], (ii) σ_1R is physically associated with NMDAR and control its negative influence on MOR [60], and (iii) σ_1R ligands showing no affinity for NMDAR were found to modulate NMDA-induced Ca^{2+} influx and NMDA-induced neuronal activity [56]. Therefore, a picture emerges whereby σ_1R modulates the activity of spinal NMDA receptors, which in turn regulate plastic adaptations associated with central sensitization. In this context, σ_1R antagonists counteract NMDAR activation.

In agreement with these results, the spinal wind-up response after repeated stimulation of C fibers is reduced in σ_1R KO mice and after the administration of σ_1R antagonists to WT mice, which is indicative of the role played by σ_1R in mechanisms underlying central sensitization and synaptic plasticity [14, 26, 83].

Altogether, these findings highlight σ_1R as a new constituent of the mechanisms modulating activity-induced sensitization in nociceptive pathways and thus as a new potential target of action for drugs designed to alleviate neuropathic pain.

8.3.4 Sigma-1 Receptor Antagonists for the Treatment of Inflammatory Pain

Inflammatory pain is largely treated with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and steroids. These agents may also be used in combination depending on the nature and chronicity of the disease. The acute inflammatory response is controlled relatively efficaciously with these drugs, however in the inflammatory pain associated with chronic diseases, such as rheumatoid arthritis, osteoarthritis or cancer, these drugs are of limited usefulness and thus a significant unmet clinical need for the treatment of chronic inflammatory pain remains.

Recently, a possible role for σ_1R in inflammatory pain has been suggested in different animal models using σ_1R KO mice and ligands (see [106] for review). The genetic inactivation of σ_1R did not alter the development of carrageenan (CARR)-induced and Complete Freund Adjuvant (CFA)-induced behavioral hypersensitivity [18]. However, pain-like responses evoked by a blunt mechanical stimulus were inhibited in the CARR-sensitized σ_1R KO mice [19]. These data indicated that the role of σ_1R on the development of behavioral hypersensitivity induced by peripheral inflammation could vary depending on the experimental conditions, especially the behavioral endpoint analyzed. Furthermore, since behavioral hypersensitivity, especially after mechanical stimulation, is attenuated in animal models of neuropathic but not inflammatory pain, a differential role for σ_1R depending on the etiology of pain (neuropathic *versus* inflammatory) is also suggested. This is not surprising since neuropathic and inflammatory pains are known to involve different pathways. Whereas the decrease in the pain threshold in inflammatory pain is due to the production of pro-inflammatory mediators, such as bradykinin, prostaglandins, leukotrienes, serotonin, histamine, substance P, thromboxanes, adenosine and ATP, protons, free radicals and cytokines [107], neuropathic pain is primarily due to direct damage of peripheral nerves, causing the continuous activity of the nociceptive fibers and subsequent peripheral and central sensitization phenomena. As mentioned in the previous section, ERK phosphorylation is a key process involved in pain sensitization pathways, the increased pERK levels in the dorsal spinal cord during neuropathy being attenuated in σ_1R KO, or after σ_1R pharmacological inhibition. However, the pain-related hypersensitivity observed in WT mice 3 h after CARR [19] or 4 days after CFA injection (data not published obtained in our laboratory), was not accompanied by a selective increase in ERK phosphorylation within the spinal cord. These results not only support the involvement of different mechanisms in the sensory hypersensitivity of experimental models of inflammatory and neuropathic pain, but also that mechanisms by which the σ_1R regulates nociception may be also different.

Regarding σ_1R ligands, the systemic and peripheral administration of different σ_1R antagonists blocked the behavioral hypersensitivity in animal models of inflammatory pain. The antihypersensitivity effect provided by E-52862 was similar to that of ibuprofen and celecoxib in both acute (CARR) and chronic (CFA) pain models. The effect was attributed to the σ_1R provided that E-52862 was devoid of effect in σ_1R KO mice [18]. Unlike anti-inflammatory agents, σ_1R antagonists exert antinociceptive but not anti-inflammatory activity, as the CARR-induced edema remained unaffected in σ_1R KO mice or after treatment with E-52862 or BD-1063 in WT mice [18, 19]. Other σ_1R antagonists, such as (−)-MRV3 and (+)-MR200 have been tested in the CARR model in rats. A dose-dependent inhibition of mechanical allodynia and thermal hyperalgesia was again observed. However, in this case, a significant reduction of the CARR-induced edema was reported with these ligands [108, 109]. Finally, a recent study describes that *N*-(2-morpholin-4-yl-ethyl)-2-(1-naphthyloxy) acetamide (NMIN) and BD-1063 were effective in the chronic constriction injury neuropathic pain model but not in the arthritic pain-induced functional impairment model in the rat [110], further suggesting a differential role of the σ_1R

depending on the type of pain, experimental conditions, and readouts.

The molecular mechanisms underlying the antinociceptive effect of σ_1R antagonists in inflammatory pain have been only partially explored. The inhibition of inflammation-induced spinal sensitization in both neurons, measured as immunoreactivity to Fos, PKC, and PKC-dependent phosphorylation of NR1, and microglia, measured as inhibition of p-p38 mitogen-activated protein kinase (MAPK) and IL-1β immunoreactivity, has been recently suggested to explain the antinociceptive effect of BD-1047 in the zymosan-induced thermal and mechanical hyperalgesia [111]. Other possible mechanisms include the modulation of bradykinin-induced Ca^{2+} release [75] and NO signaling [112], both key mediators released during inflammation and contributing to the peripheral sensitization, which are enhanced by σ_1R activation.

Regulating excitability of peripheral afferents is being pursued as a possible strategy to manage pathological pain [113, 114]. This "peripheral strategy" is of particular interest because of the potential of developing novel drugs that do not access central sites, or to deliver drugs locally by topical or other application methods. Both approaches avoid central exposure to drugs and have thus the potential to reduce side effects compared to systemic administration of drug crossing the blood-brain barrier. The role of peripheral σ_1R in inflammatory pain has been recently studied by Tejada et al. [19]. These authors have identified peripheral σ_1Rs as a key sites contributing to the antinociceptive effect of σ_1R antagonists to ameliorate inflammatory hyperalgesia. They found that intraplantar administration of several σ_1R antagonists in the inflamed paw was sufficient to completely reverse hyperalgesia and that the σ_1R agonist PRE-084 blocked the systemically-induced antinociceptive effect of selective σ_1R antagonists in the CARR pain model. The role of peripheral σ_1R is supported by its high density in DRGs [11]. The contribution of the peripheral σ_1R in types of pain other than inflammatory merits further studies.

8.3.5 Sigma-1 Receptor Antagonists for the Treatment of Other Types of Pain

8.3.5.1 Visceral Pain

Visceral pain is the most frequent type of pathological pain and one of the main reasons for patients to seek medical assistance [115]. However, most of our knowledge about pain mechanisms derives from experimental studies of somatic (principally cutaneous) pain rather than visceral pain. The associated symptoms, pathophysiological mechanisms, and response to drug treatment of visceral and somatic pain are different; consequently, it is not valid to indiscriminately extrapolate findings from the somatic–cutaneous to the visceral domain [116]. In spite of its importance, very few papers have addressed the role of σ_1R in visceral pain. In this regard, González-Cano and co-workers [16] evaluated the role played by σ_1R in the intracolonic capsaicin-induced visceral pain model, measuring both pain-related behaviors and referred mechanical hyperalgesia to the abdominal wall. The intracolonic administration of capsaicin induced concentration-dependent visceral pain-related behaviors and referred hyperalgesia in both WT and σ_1R-KO mice, but the maximum number of pain-related behaviors induced by 1 % capsaicin was roughly 50 % in the σ_1R-KO mice compared to the WT. Several σ_1R antagonists (BD-1063, E-52862 and NE-100) administered subcutaneously dose-dependently reduced the number of behavioral responses and reversed the referred mechanical hyperalgesia to control thresholds in WT mice. These compounds were inactive in the σ_1R-KO mice, thus confirming the σ_1R-mediated effect.

8.3.5.2 Orofacial Pain

Some of the most prevalent and debilitating pain conditions arise from the structures innervated by the trigeminal system (head, face, masticatory musculature, temporomandibular joint and associated structures) [117]. Orofacial pain disorders are highly prevalent and debilitating conditions involving the head, face, and neck. These condi-

tions represent a challenge to the clinician since the orofacial region is complex and pain can arise from many sources. According to Okeson [118], orofacial pain is divided into physical and psychological conditions. Physical conditions comprise: (i) temporomandibular disorders, which include disorders of the temporomandibular joint and disorders of musculoskeletal structures (e.g., masticatory muscles and cervical spine); (ii) neuropathic pains, which include episodic (e.g., trigeminal neuralgia) and continuous (e.g., peripheral/centralized mediated) pains; and (iii) neurovascular disorders, including migraine. Psychological alterations include mood and anxiety disorders.

The role of σ_1R in orofacial pain has been addressed by Kwon et al., who described attenuation of pain behavior (face grooming) after BD-1047 administration in a model of headache pain induced by intracisternal capsaicin administration in rats [119]. Moreover, the σ_1R antagonist BD-1047 consistently reduced capsaicin-induced Fos-like immunoreactivity and the phosphorylation of the NR1 subunit of the NMDAR in the trigeminal nucleus caudalis (TNC) in a dose-dependent manner. As intracranial headaches, including migraines, are mediated by nociceptive activation of the TNC, the authors propose that the use of σ_1R antagonists may be a promising strategy for the treatment of headache disorders. In the same way, Pyun et al. reported that chronic activation of σ_1R by intracisternal administration of the σ_1R agonist PRE084 produced TNC neuronal activation as a migraine trigger in rats. Accordingly, chronic (over 7 days) intracisternal injection of PRE-084 produced sustained neuronal activation (measured as Fos and ΔFosB immunoreactivity) accompanied by increased neuronal susceptibility (measured as phosphorylation of the NMDAR and ERK) in the TNC, which correlated with an increase in face grooming/scratching behavior [120]. The authors pointed out the possible role of neurosteroids in migraine triggering in humans, as migraine is three times more common in women than in men, and frequently evokes pain during the low progesterone peri-menstrual phase [121]. Consistently, systemic injection of the σ_1R antagonist progesterone reduced migraine symptoms in both humans and animals [122, 123], whereas other neurosteroids behaving as σ_1R agonists, including dehydroepiandrosterone, have a pronociceptive role [124].

Roh et al. showed that intraperitoneal BD-1047 administration reduced nociceptive responses (rubbing with the ipsilateral fore- or hind-paw) in the mouse formalin orofacial pain model (5 % formalin, 10 μL subcutaneously injected into the right upper lip) [125]. BD-1047 also reduced the number of Fos-immunoreactive cells and p-p38 MAPK in the ipsilateral TNC, whereas the number of immunoreactive p-ERK cells was not modified. Using the same model, Yoon et al. demonstrated that the co-administration of clonidine with BD-1047 enhanced low-dose clonidine-induced antinociceptive effects without the sedation and hypotension side effects typically found after the administration of clonidine alone at analgesic doses. Interestingly, co-localization for α_{2A} adrenoceptors and σ_1R receptors was demonstrated in trigeminal ganglion cells [97].

8.3.5.3 Ischemic Pain

The contribution of peripheral σ_1R to ischemic pain has been recently demonstrated in a rat model of hindlimb thrombus-induced mechanical allodynia. σ_1R expression significantly increased in skin, sciatic nerve and DRG at 3 days post thrombus-induced ischemic pain in rats. Authors suggested a facilitatory effect of σ_1R on acid-sensing ion channels (ASICs) and purinergic P_2X receptors, as intraplantar injection of the σ_1R antagonist BD-1047 reduced mechanical allodynia synergistically with the ASIC blocker amiloride and the P_2X antagonist TNP-ATP [42].

8.3.5.4 Postoperative Pain

Gris et al. [126] compared the time course for thermal hyperalgesia and mechanical allodynia induced by paw incision in WT and σ_1R KO mice. No differences were found in the acquisition of thermal hyperalgesia, but σ_1R KO mice showed a faster recovery of mechanical sensitivity back to normal thresholds. c-Fos immunoreactivity was induced in the ipsilateral dorsal horn

of the spinal cord in WT mice and it was attenuated in the σ_1R KO mice 4 h after surgery. The administration of morphine and the σ_1R antagonist E-52862 4 h after surgery produced a dose-dependent antinociceptive effect, whereas ibuprofen and celecoxib were ineffective. E-52862 showed no effect in σ_1R KO mice, thus confirming the involvement of σ_1R in E-52862-mediated effects. Thus, the σ_1R seems to be involved in the sensitization to noxious stimulus induced by surgery in mice, pointing at the potential use of selective σ_1R antagonists to alleviate postoperative pain.

8.4 Concluding Remarks

The effects reported with σ_1R ligands (pronociceptive in the case of agonists and antinociceptive in the case of antagonists) are consistent with a role for σ_1R in central sensitization and pain hypersensitivity and suggest a potential therapeutic use of σ_1R antagonists for the management of neuropathic pain and other pain conditions including inflammatory, visceral, ischemic, postoperative and orofacial pain. The σ_1R seems to be devoid of its own specific signaling machinery, but it acts as a modulator of the intracellular signaling incurred upon activation of several receptors, enzymes, and ion channels relevant in pain transmission and processing. Ligands acting on σ_1R can amplify or reduce the signaling initiated when the target protein the σ_1R is interacting with becomes activated, but they are *per se* inactive. On this basis, σ_1R ligands have been postulated as ideal therapeutic drugs, effective only under pathological conditions, but inactive in normal resting/healthy conditions. Thus, while having no effects by themselves under normal physiological conditions, σ_1R ligands exert their modulatory activity under conditions involving a disturbance, such as chronic pain. This concept is very important in terms of safety and tolerability, as an ideal analgesic drug should be able to modify the stressed/dysfunctional pathway without affecting normal physiological functions. In the case of σ_1R antagonists, no adverse events have been described in rodents at doses exerting antinociceptive effects based on preclinical studies. Unlike other analgesics (e.g., opioids), σ_1R antagonists do not modify the normal sensory perception, and normal/baseline nociceptive thresholds are not modified when σ_1R antagonists are administered to normal animals. Only when the system is sensitized and hypersensitivity (i.e., allodynia and hyperalgesia) occurs following prolonged noxious stimulation (e.g., capsaicin or formalin injection) or persistent abnormal afferent input (e.g., nerve injury or inflammation) does the σ_1R antagonist exert its effect: reversion of the diminished pain thresholds back to normal sensitivity thresholds. Accordingly, σ_1R antagonists are not strictly analgesics; they are antiallodynic and antihyperalgesic drugs. Moreover, there is plenty of data supporting the combination of σ_1R antagonists with opioid therapy, which may result in a potentiation of opioid analgesia without significant increase of unwanted effects. This would result in using lower doses of opioids, with less side effects but efficacious based on the enhancement of the analgesic effect if σ_1R antagonists are used as opioid adjuvants.

Overall, based on preclinical data, the use of selective σ_1R antagonists could represent a promising efficacious and safe strategy to approach difficult-to-treat chronic pain conditions including neuropathic pain, and to enhance (or maintain) analgesic efficacy and increase the safety margin of opioids. In this regard, the most advanced investigational σ_1R antagonist, E-52862 showed a good safety, tolerability and pharmacokinetic profile in phase I studies [84]. The outcome of clinical studies with E-52862 will be of great interest to ascertain the potential of this new therapeutic approach to pain management.

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