# Sigma-1 Receptor and 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 respect to existing therapies and/or reduce their unwanted effects. Current preclinical evidence supports the modulatory role of the sigma-1 receptor ($\sigma_1$R) in nociception, mainly based on the pain-attenuated phenotype of $\sigma_1$R knockout mice and on the antinociceptive effect exerted by $\sigma_1$R

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antagonists on pain of different etiology, very consistently in neuropathic pain, but also in nociceptive, inflammatory, and visceral pain. $\sigma_1$R is highly expressed in different pain areas of the CNS and the periphery, particularly dorsal root ganglia (DRG), and interacts and modulates the functionality of different receptors and ion channels. Accordingly, antinociceptive effects of $\sigma_1$R antagonists both acting alone and in combination with other analgesics have been reported at both central and peripheral sites. At the central level, behavioral, electrophysiological, neurochemical, and molecular findings support a role for $\sigma_1$R antagonists in inhibiting augmented excitability secondary to sustained afferent input. Moreover, the involvement of $\sigma_1$R in mechanisms regulating pain at the periphery has been recently confirmed. Unlike opioids, $\sigma_1$R antagonists do not modify normal sensory mechanical and thermal sensitivity thresholds but they exert antihypersensitivity effects (antihyperalgesic and antiallodynic) in sensitizing conditions, enabling the reversal of nociceptive thresholds back to normal values. These are distinctive features allowing $\sigma_1$R antagonists to exert a modulatory effect specifically in pathophysiological conditions such as chronic pain.

**Keywords**
Allodynia • Analgesia • Antinociception • Chronic pain • E-52862 • Hyperalgesia • S1RA • Sigma-1 receptor

## 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 (Jamieson et al. 2014). Conversely, chronic pain has been recognized as pain that persists beyond normal healing time and hence lacks the acute warning function of physiological nociception. Chronic pain, defined as pain lasting or recurring for more than 3–6 months, may be associated with many common diseases or considered 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 (Treede et al. 2015). Moreover, chronic pain is accompanied with other comorbidities, such as depression, deeply affecting patient's quality of life. Unfortunately, currently available treatments provide the modest improvements in pain and minimum improvements in physical and emotional functioning (Turk et al. 2011). Thus, the unmet medical need in the pain area is huge, and particularly relevant in difficult-to-treat pain modalities, such as neuropathic pain.

Despite massive efforts coming from basic science and clinical research, pain management remains a clinical challenge, with many patients still suffering with unrelieved or undertreated pain. There is a lack of real breakthrough innovation in the field (Kissin 2010; Labianca et al. 2012) and thus a need for new drugs acting through new mechanisms of action, which could increase the efficacy of existing therapies and/or reduce their unwanted effects.

The sigma-1 receptor ($\sigma_1$R), a unique ligand-regulated chaperone protein with no precedent and no homology to known proteins (Almansa and Vela 2014), has become one among the new and most promising pharmacological targets in pain. $\sigma_1$R was found to be unique, with no significant similarity with any other known mammalian protein receptors, and to have about 90% amino acid identity and 95% similarity across species (Hanner et al. 1996; Kekuda et al. 1996; Seth et al. 1997). From a functional point of view, the $\sigma_1$R physically interacts with a variety of receptors and ion channels or elements of their transduction machinery and acts as a modulator of their activity. At the endoplasmic reticulum, the $\sigma_1$R acts as a ligand-operated molecular chaperone regulating $Ca^{2+}$ flow via inositol 1,4,5-trisphosphate ($IP_3$) receptors (Hayashi and Su 2007; Su et al. 2010). $\sigma_1$Rs, through their molecular chaperone activity, regulate protein folding/degradation, oxidative stress, and cell survival (see Hayashi (2015) for a review). In the plasma membrane, $\sigma_1$R interacts with components of the plasma membrane-bound signal transduction to modulate the activity of neurotransmitter receptors and ion channels, including $K^+$ channels, $Ca^{2+}$ channels, *N*-methyl-D-aspartate receptor (NMDAR), and opioid receptors (see Zamanillo et al. (2013) for a review). Interestingly, its activity can be modulated (enhanced or inhibited) by $\sigma_1$R ligands in an agonist–antagonist manner.

The purpose of this review is to summarize the current knowledge on the involvement of $\sigma_1$R in pain modulation. First, regarding the site of action, the role of $\sigma_1$R in central sensitization phenomena has been reported at the behavioral, electrophysiological, neurochemical, and molecular levels. In contrast, the involvement of $\sigma_1$R in mechanisms regulating pain at the periphery has been recently confirmed and requires further investigation. Second, due to the chaperoning activity of the $\sigma_1$R, the current understanding of its interaction with different other molecular targets involved in pain transduction, transmission, and processing is summarized. Third, we have addressed the role of $\sigma_1$R in pain gathering at the experimental level using genetic approaches, i.e., by the use of $\sigma_1$R knockout (KO) mice or antisense probes, as well as pharmacological tools, including nonselective marketed drugs and experimental drugs in discovery and clinical development phases. The use of $\sigma_1$R KO mice has been critical to identify the $\sigma_1$R as a modulator of activity-induced sensitization of pain pathways. Accordingly, $\sigma_1$R KO mice are insensitive or show attenuated expression of pain behaviors in chemically induced (e.g., formalin and capsaicin) and neuropathic pain models (Cendan et al. 2005b; Entrena et al. 2009b; de la Puente et al. 2009; Nieto et al. 2012, 2014; Gonzalez-Cano et al. 2013; Gris et al. 2014; Tejada et al. 2014). These genetic as well as pharmacological findings using several $\sigma_1$R ligands (see Vela et al. (2015) for a review) provided evidence to consider $\sigma_1$R antagonists as an innovative and alternative approach for treating pain, especially neuropathic pain but also other sensitizing pain conditions. Notwithstanding the foregoing, several discrepancies between the information coming from the $\sigma_1$R KO mice and pharmacological approaches have been reported and the possible causes are discussed.

Preclinical evidence has pointed out their potential as an adjuvant therapy to enhance opioid analgesia, without increasing the side effects associated with opioid use (Chien and Pasternak 1994; Vidal-Torres et al. 2013; Sanchez-Fernandez et al. 2013, 2014). The modulation of opioid system by the $\sigma_1$R is fully covered in another

chapter of this book. As an advantage over opioids, $\sigma_1$R 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, $\sigma_1$R 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 (Chien and Pasternak 1995; Kim et al. 2008; Entrena et al. 2009b; Romero et al. 2012). Among the $\sigma_1$R antagonists, E-52862 (also known as S1RA) is the leading compound in the field and the only currently being developed for the treatment of pain. It was identified in a medicinal chemistry program as a highly active and selective $\sigma_1$R antagonist (Diaz et al. 2012). It was safe, well-tolerated, and showed good pharmacokinetic profile following oral administration to human volunteers in phase I studies (Abadias et al. 2013) and it is currently undergoing Phase II clinical trials for the treatment of different types of pain.

## 2 Localization of $\sigma_1$R in Relation to Pain Transmission: Central Vs Peripheral

$\sigma_1$R is expressed in several areas of the CNS specialized in nociceptive signaling processing, including the dorsal horn (DH) of the spinal dorsal cord, thalamus, periaqueductal gray (PAG), basolateral amygdala, and rostroventral medulla (RVM) (Alonso et al. 2000; Phan et al. 2005). $\sigma_1$R is also expressed in peripheral dorsal root ganglia (DRG) neurons (Guitart et al. 2004; Bangaru et al. 2013). Importantly, its high density in DRG, in which $\sigma_1$R expression is roughly an order of magnitude higher than in several CNS areas involved in pain signaling, points to a functional role of peripheral $\sigma_1$R in pain modulation (Sanchez-Fernandez et al. 2014). $\sigma_1$R is expressed by both sensory neurons and satellite cells in rat DRGs and its expression is regulated in axotomized neurons and in accompanying satellite glial cells (Bangaru et al. 2013). In accordance with $\sigma_1$R anatomical distribution, the antinociceptive effects of $\sigma_1$R antagonists both when acting alone and in combination with opioids to enhance opioid analgesia have been reported at both central and peripheral sites. A systematic review of $\sigma_1$R-dependent central and peripheral mechanisms in pain processing and development can be found in Romero et al. (2016).

### 2.1 Effect of $\sigma_1$R Antagonists at Central Sites: Inhibitory Effect on Central Sensitization

Central sensitization is responsible for many of the temporal, spatial, and threshold changes in pain sensibility and exemplifies the fundamental contribution of the CNS to the generation of pain hypersensitivity. Central sensitization results from changes in the properties of neurons in the CNS. Thus, pain is no longer coupled to the presence, intensity, or duration of noxious peripheral stimuli as it occurs in acute nociceptive

pain. Instead, central sensitization produces pain hypersensitivity by exaggerating the sensory response elicited by nociceptive suprathreshold stimuli and allowing the response to subthreshold stimuli, including those that usually evoke innocuous sensations (D'Mello and Dickenson 2008).

An inhibitory effect has been attributed to $\sigma_1$R antagonism on central sensitization phenomena, as supported at the behavioral (animal pain models), electrophysiological (spinal wind-up recordings), neurochemical (spinal release of neurotransmitters), and molecular (NMDAR function regulation) levels. Activation of primary afferent nociceptive fibers subsequent to intradermal injection of some chemical irritants, including capsaicin or formalin, into the plantar skin of the hind paw in rodents or into the skin of humans produces acute/immediate nociceptive behaviors followed by long-lasting, secondary mechanical hypersensitivity (e.g., mechanical allodynia) that results from central sensitization (O'Neill et al. 2012). Interestingly, capsaicin was unable to induce mechanical hypersensitivity in $\sigma_1$R KO mice, and the effect in $\sigma_1$R KO mice was mimicked in wild-type (WT) animals treated with BD1063, BD1047, or NE100, three $\sigma_1$R antagonists which dose-dependently inhibited capsaicin-induced mechanical allodynia (Entrena et al. 2009b). Other $\sigma_1$R antagonists including haloperidol and its metabolites I and II (Entrena et al. 2009a), E-52862 (Romero et al. 2012) and some spirocyclic thiophene bioisosteres (Oberdorf et al. 2008), 1′-benzyl-3-methoxy-3H-spiro[[2]benzofuran-1,4′-piperidine] (Wiese et al. 2009), and a 1,3-dioxane ligand 2 (Utech et al. 2011) also produced antiallodynic effects in the capsaicin model. In addition, the $\sigma_1$R agonist PRE-084 reversed the effect of antagonists (Entrena et al. 2009a, b), further supporting the role played by $\sigma_1$R in capsaicin-induced central sensitization phenomena. In the formalin-induced pain model in mice, both phases of pain were reduced by approximately 55% in mice lacking $\sigma_1$R in comparison to WT animals (Cendan et al. 2005b). Shortly after this study, the same authors reported that haloperidol and its metabolites I and II, which have affinity for $\sigma_1$R, dose-dependently inhibited formalin-induced pain in mice through a mechanism likely involving antagonism on $\sigma_1$R (Cendan et al. 2005a). Subsequent studies using selective and prototypical $\sigma_1$R antagonists such as E-52862 (Romero et al. 2012; Vidal-Torres et al. 2014) and BD1047 (Kim et al. 2006), and novel $\sigma_1$R antagonists based on pyrimidine (Lan et al. 2014a) or 3,4-dihydro-2(1H)-quinolinone (Lan et al. 2014b) scaffolds corroborated these initial findings and pointed to the spinal cord and supraspinal CNS regions as sites for the $\sigma_1$R-mediated modulation of formalin sensitization. The spinal cord was first pointed out in the study by Kim et al. in mice, where intrathecal (i.t.) pretreatment with the $\sigma_1$R antagonist BD1047 dose-dependently reduced formalin-induced pain behaviors in the second phase, but not in the first phase of the formalin test, concomitant with reduced formalin-evoked Fos expression in spinal DH neurons (Kim et al. 2006). In addition to the spinal cord, supraspinal sites were supported by the finding in rats that i.t. pretreatment with E-52862 attenuated the formalin-induced flinching behavior, but not lifting/licking behaviors, whereas E-52862 also attenuated lifting/licking when intracerebroventricularly (i.c.v.) injected (Vidal-Torres et al. 2014). In this way, it is interesting to note that flinching is a spinal response whereas lifting/licking behaviors are supraspinal responses (Coderre et al. 1994), and that both spinal and supraspinal descending modulation of central neural plasticity occur in formalin-induced pain (Coderre et al. 1994;

Vaccarino and Chorney 1994). Therefore, it is concluded that $\sigma_1$R acts in the CNS at both spinal and supraspinal sites to modulate pain sensitization following sustained peripheral activation of nociceptors by formalin.

## 2.2 Effect of $\sigma_1$R Antagonists at Peripheral Sites: Inhibitory Effect on Peripheral Sensitization

Increasing evidence suggests that activity from the periphery is essential, not only to initiate but also to maintain pain (Richards and McMahon 2013). Experience from clinical studies using lidocaine and capsaicin patches, local steroids, and regional anesthesia, among others, clearly demonstrates that blocking the peripheral nociceptive input is an effective strategy to relieve chronic pain. Studies focused on finding new analgesic strategies with a peripheral site of action merit further efforts, as targeting the periphery could be a good approach to overcome the typical side effects related to CNS actions of current analgesics.

Although the role of peripheral $\sigma_1$R in pain has not been extensively studied (Tejada et al. 2014), recent pieces of information are actually confirming their involvement in mechanisms regulating pain, both when administered alone or in combination with opioids. Systemic administration of the selective $\sigma_1$R antagonist E-52862 produced an attenuation of the flinching and lifting/licking behaviors in the formalin test in rats, which was concomitant with an enhancement of noradrenaline levels and a reduction of formalin-evoked glutamate release in the spinal DH. Although a supraspinal effect was confirmed by the local (i.c.v) administration of E-52862, a peripheral contribution was also shown. In fact, intraplantar (i.pl.) administration of E-52862 in the ipsilateral paw (but not in the contralateral) reduced lifting/licking behaviors in phase I and II of the formalin test (Vidal-Torres et al. 2014).

Recent studies have also evaluated the role of $\sigma_1$R in inflammatory pain (Gris et al. 2014; Parenti et al. 2014; Tejada et al. 2014; for review see Gris et al. (2015)). Systemic administration of several $\sigma_1$R antagonists was effective in the carrageenan- and complete Freund adjuvant-induced pain models. Particularly, the study by Tejada et al. described the importance of peripheral $\sigma_1$R in the carrageenan-induced pain model in mice. The local (i.pl.) administration of the $\sigma_1$R agonist PRE-084 abolished the systemic antihypersensitive effect of the $\sigma_1$R antagonists BD1063 and E-52862. Moreover, the i.pl. administration of the $\sigma_1$R antagonist E-52862 in the inflamed paw was sufficient to completely reverse inflammatory hyperalgesia. The antihyperalgesic effect of locally administered E-52862 was reverted by the i.pl. administration of the $\sigma_1$R agonist PRE-084 and was absent in $\sigma_1$R KO mice, thus confirming that the peripheral antihyperalgesic effect of E-52862 was mediated through $\sigma_1$R. As a conclusion, a number of reports have revealed the possibility of targeting peripheral $\sigma_1$R to ameliorate inflammatory hyperalgesia (Gris et al. 2015; Tejada et al. 2014). A peripheral $\sigma_1$R-related mechanism might be more relevant in the modulation of inflammatory pain than in pain evoked by other etiologies because this type of pain is characterized by a pronounced enhancement of nociceptor responsiveness (peripheral sensitization) in response to the inflammatory mediators released at the inflammation site (Xu and

Yaksh 2011). Due to its pleiotropic chaperoning nature and acting downstream to the activation of different receptors and channels, $\sigma_1$R could modulate the intracellular signaling of a variety of pro-algesic mediators released at the inflamed site. Among them, bradykinin and nitric oxide (NO) are key mediators released during inflammation contributing to peripheral sensitization (Wang et al. 2006; Petho and Reeh 2012). $\sigma_1$R activation enhances both bradykinin-induced $Ca^{2+}$ signaling in neuronal-like cell cultures (Hayashi et al. 2000) and NO signaling (Roh et al. 2011). In addition, pain sensitization after peripheral inflammation involves plastic changes mediated by an increase in spinal excitatory neurotransmission together with activation of kinases, including ERK1/2, which are known to be modulated by $\sigma_1$R (de la Puente et al. 2009).

In addition to inflammatory pain, the contribution of peripheral $\sigma_1$R to ischemic pain has been recently demonstrated in a rat model of hind limb thrombus-induced mechanical allodynia (Kwon et al. 2016). $\sigma_1$R expression significantly increased in skin, sciatic nerve, and DRG at 3 days post-thrombus-induced ischemic pain in rats. Authors suggested a facilitating effect of $\sigma_1$R on acid-sensing ion channels (ASICs) and purinergic P2X receptors, as i.pl. injection of the $\sigma_1$R antagonist BD1047 reduced mechanical allodynia synergistically with the ASIC blocker amiloride and the P2X antagonist TNP-ATP (Kwon et al. 2016). Regarding neuropathic pain, $\sigma_1$R antagonism has been shown to restore injury-induced decrease in voltage-gated $Ca^{2+}$ current in dissociated rat DRG neurons following spinal nerve ligation but had no effect on control and non-injured DRGs, which is discussed as an antinociceptive mechanism as inward $Ca^{2+}$ currents are required for natural suppression of repetitive firing via opening of $Ca^{2+}$-activated $K^+$ channels (Pan et al. 2014).

## 3 Neuroprotective Effects of $\sigma_1$R Antagonists in Relation to Pain

Neuroprotective but also neurotoxic roles have been attributed to $\sigma_1$R in the CNS by mechanisms involving modulation of cellular $Ca^{2+}$ homeostasis, excitotoxicity, oxidative and nitrosative damage, and endoplasmic reticulum and mitochondrial stress. Indeed, both $\sigma_1$R agonists (DeCoster et al. 1995; Shimazu et al. 2000; Vagnerova et al. 2006; Mancuso et al. 2012; Griesmaier et al. 2012) and antagonists (DeCoster et al. 1995; Shimazu et al. 2000; Schetz et al. 2007; Luedtke et al. 2012) have been reported to exert protective effects on neurons using different in vitro and/or in vivo experimental approaches. In the context of pain, it has been reported that $\sigma_1$R antagonism exerts a preventive effect against peripheral neuropathy. In particular, genetic inactivation ($\sigma_1$R KO mice) and pharmacological blockade of $\sigma_1$R prevented paclitaxel-induced sensory nerve mitochondrial abnormalities, concomitant with the prevention of paclitaxel-induced cold and mechanical allodynia (Nieto et al. 2014). In contrast, the $\sigma_1$R agonist SA4503, but not the $\sigma_1$R antagonist NE100, produced antinociceptive effects against chemotherapeutic-induced neuropathic pain in rats (Tomohisa et al. 2015). Mitochondrial function/dysfunction has been suggested as a causal or contributory mechanism of normal sensory processing and chronic pain, not only in painful peripheral neuropathies evoked by chemotherapy but also in diabetes and HIV (Flatters 2015). $\sigma_1$Rs at the

endoplasmic reticulum–mitochondrion contact are known to regulate mitochondrial function, including intramitochondrial $Ca^{2+}$ homeostasis, oxidative stress, and cellular bioenergetics (Su et al. 2010; Hayashi 2015). The role played by $\sigma_1$R in regulating pain-related mitochondrial dysfunction merits further investigation.

## 4 $\sigma_1$R Pain Interactome

The $\sigma_1$R, as a ligand-operated chaperone, is able to interact with other proteins including receptors, enzymes, or ion channels, many of which are involved in nociception. Figure 1 shows the known regions of the $\sigma_1$R that are involved in its direct interaction with other protein partners. In the receptor's N terminal part, there appears to be the interaction motifs for the NMDAR NR1 subunit, as well as the small five-amino acid dimerization motif for the $\sigma_1$R (Rodriguez-Munoz et al. 2015). Whether other interacting partners, like, for instance, ion channels described to interact with the $\sigma_1$R, do use this N terminal part of the receptor is still unknown. Interestingly, in the other part of the receptor, the C terminal part comprising from the transmembrane domain, several proteins share the same interaction region with the $\sigma_1$R (Ortega-Roldan et al. 2013; Su et al. 2016). These proteins are the ankyrin B, BiP, and $IP_3$ receptors that along with the $\sigma_1$R play important roles in endoplasmic reticulum $Ca^{2+}$ homeostasis. Also, as explained above, while in control situations the $\sigma_1$R interacts mainly with ankyrin B and BiP, a reduction of these interactions and an increase in the interaction with $IP_3$ receptors are observed following a pathological stress insult (Su et al. 2016). These data point out that ankyrin B, BiP, and $IP_3$ receptors are competing each other for their binding with the $\sigma_1$R and that some interactions prevail over the others depending on the surrounding intracellular environmental conditions. Also, although the interaction region with these proteins is relatively large and the particular amino acids involved in each of them are not completely known, the fact that this competition exists between them suggests that at least part of those interaction regions must be shared. Interestingly, this competition is regulated as well by $\sigma_1$R ligands. New information regarding the interaction motifs of $\sigma_1$R partners to know better which regions of the receptor are responsible for chaperone activity and which partners can interact simultaneously or through a competitive manner is needed.

Pain is a very complex pathological condition and either nociceptive or neurogenic pain involves various interactive mechanisms at different neuronal levels such as peripheral nociceptors, spinal cord, or supraspinal levels. At all those levels, many chemical mediators and their molecular targets are engaged to code for and transmit the pain sensation (Millan 1999). $\sigma_1$R, playing its role as a chaperone protein, has been implicated in the regulation of many of those other molecular targets, including receptors, enzymes, and ion channels that are involved in pain sensation and transmission. Our objective in this section is to summarize $\sigma_1$R molecular partners, linking the regulation of these interactions to nociception, and thus describing the $\sigma_1$R pain interactome.

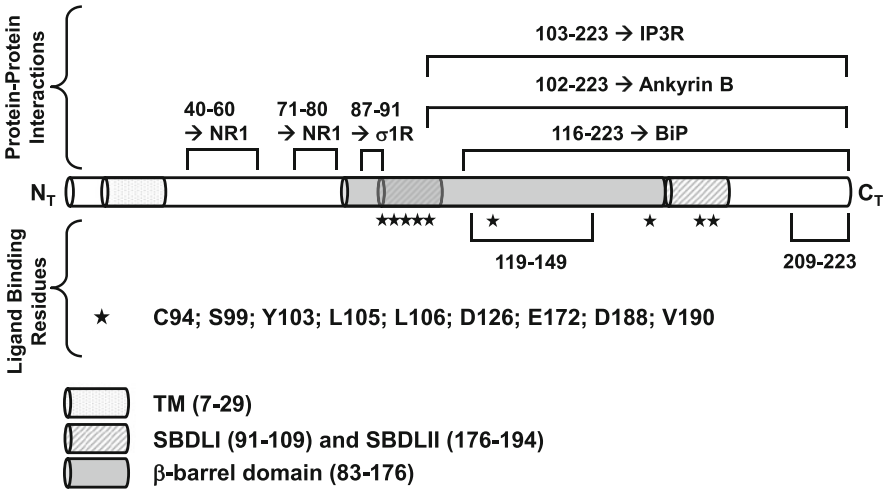


**Fig. 1** Diagram of known sigma-1 receptor ($\sigma_1$R) motifs involved for interaction with their molecular partners and residues involved in ligand recognition. Protein–protein interaction domains are represented above the $\sigma_1$R sequence diagram, while the residues involved in ligand recognition are represented below. Regions of the $\sigma_1$R that mediate the interaction with the NR1 subunit of NMDA receptors and its oligomerization are comprised in the N terminal part of the receptor delimited till the first sterol binding domain. The C terminal part of the $\sigma_1$R starting from the first sterol binding domain is a region of the receptor clearly involved in its chaperone role as it serves to interact with proteins such as the $IP_3$ receptors, BiP, and ankyrin B. The recently described unique transmembrane domain (TM) and the β-barrel domain, which is involved in ligand-binding, and both steroid binding domains (SBDLs) are also depicted (Schmidt et al. 2016). Studies involving deletion of the 119–149 or 209–223 amino acid regions, mutations, or photolabeling of C94, S99, Y103, L105, L106, D126, E172, D188, and V190 have implicated all these amino acids in ligand recognition

## 4.1 Ion Channels

### 4.1.1 Voltage-Gated Sodium Channels

Nociceptors detect noxious stimuli and transmit this sensation to the CNS by means of action potentials. The fast upstroke of the action potential is generated through sodium channel activation (Liu and Wood 2011). A direct interaction of $\sigma_1$R with neuronal sodium channels has not been described yet, but $\sigma_1$Rs have been shown to co-immunoprecipitate with Nav1.5, the cardiac sodium channel, when transfected in tsA201 cells (Balasuriya et al. 2012). Both the nonselective $\sigma_1$R antagonist haloperidol and the $\sigma_1$R agonist (+)-pentazocine have been described to disrupt the $Na_v1.5$/$\sigma_1$R interaction, haloperidol being more effective in reducing this interaction (Balasuriya et al. 2012). Accordingly, independent on the agonistic or antagonistic nature of ligands, $\sigma_1$R agonists (+)-SKF-10047 and (+)-pentazocine and nonselective $\sigma_1$R/$\sigma_2$R 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 (Johannessen et al. 2009). 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 $\sigma_1$ and/or $\sigma_2$ receptors, and in some cases by $\sigma_1$R knockdown with small interfering RNA (Johannessen et al. 2011). Similarly, patch-clamp experiments in isolated intracardiac neurons from neonatal rats revealed that the nonselective $\sigma_1$R/$\sigma_2$R agonist DTG and the $\sigma_1$R selective agonist (+)-pentazocine inhibited voltage-gated sodium channels. The selective $\sigma_1$R antagonist BD1063 did not modulate the current but inhibited DTG block of sodium currents by ~50%, suggesting that the effects involve, at least in part, $\sigma_1$Rs (Zhang et al. 2009). Action potential generation through very fast inactivating sodium current is followed by a non-inactivating or persistent current that normally comprises about 5% of the whole sodium current generated. This persistent sodium current has been involved in the setting of the membrane resting potential in a subthreshold range regulating repetitive firing and enhancing synaptic transmission (Kiss 2008). $Na_v1.8$ is a tetrodotoxin-resistant voltage-gated sodium ion channel that is expressed specifically in the DRG, in small-diameter unmyelinated sensory neurons, and is involved in nociception. It has been described that human $Na_v1.8$ channel displays slower inactivation kinetics and a larger persistent current than already described for this channel in other species (Han et al. 2015). It is tempting to speculate that the interaction of $\sigma_1$R 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 $\sigma_1$R 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, $\sigma_1$R 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 $\sigma_1$R-independent mechanism (Gao et al. 2012).

### 4.1.2 Voltage-Gated Potassium Channels

While sodium channels play a very prominent role in action potential generation producing depolarization, potassium counterparts play the opposite role leading to repolarization. The opening of potassium channels generates a hyperpolarizing potassium efflux across the membrane that counteracts inward ion conductance to limit neuronal excitability and firing rate (Tsantoulas and McMahon 2014). Not surprisingly, a role for potassium channels in nociceptive processing has been described (Tsantoulas and McMahon 2014). Cell lysates from nucleus accumbens medial shell tissue immunoprecipitated with specific $K_v1.2$ antibodies were shown to co-immunoprecipitate the $\sigma_1$R (Kourrich et al. 2013). This interaction was further confirmed in double transfected NG108-15 cells. $K_v1.2$ are delayed rectifier channels activated by slight membrane depolarization and are involved in the transient slowly inactivating potassium currents $I_D$. In CNS neurons, $K_v1.2$ channels are mainly localized at the axon initial segment where they modulate action potential threshold and firing rates, as well as nerve terminals where they control neurotransmitter release. In the peripheral nervous system, $K_v1.2$ are found in the soma and juxtaparanodes of medium-large DRG

neurons and are largely decreased after axotomy what may contribute to the hyperexcitable phenotype observed after such type of injury. Diminished $K_v1.2$ activity contributes to mechanical and cold neuropathic pain by depolarizing the resting membrane potential, reducing threshold current, and augmenting firing rates in myelinated neurons (Tsantoulas and McMahon 2014). Aydar and colleagues using co-immunoprecipitation techniques demonstrated a direct interaction with the $K_v1.4$ subtype in transfected xenopus oocytes and in rat posterior pituitary tissue. Not only a $\sigma_1R$ agonist could elicit a decrease in $K_v1.4$ conductance in double transfected oocytes but also the expression of the $\sigma_1R$ altered the functional activity of $K_v1.4$ expressed in these cells. In the presence of co-expressed $\sigma_1R$, $K_v1.4$ inactivated at a faster rate, and although net current efflux was also diminished, the voltage dependence of channel activation showed no change (Aydar et al. 2002). $\sigma_1R$ agonists could elicit a decrease in $K_v1.4$ conductance in double transfected oocytes, but the co-expression of $\sigma_1R$ 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 $K_v1.4$ suggest a function for $\sigma_1R$ as auxiliary subunits for voltage-activated potassium channels (Kourrich et al. 2013). 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 (Rasband et al. 2001). The regulation of this subtype of potassium channel by $\sigma_1R$ in this particular type of nociceptors is consistent with the regulatory role that $\sigma_1R$ plays in pain modulation.

### 4.1.3 Voltage-Gated Calcium Channels

Voltage-gated calcium channels (VGCC) are other ion channels involved in neuronal action potentials that contribute to pain pathophysiology (Perret and Luo 2009). They are comprised of five different families, N, T, L, P/Q, and R-type, all of which are present at some extent at the central and peripheral nervous system playing a role in neurotransmitter release, membrane depolarization and hyperpolarization, enzyme activation and inactivation, and gene regulation (Perret and Luo 2009). Tchedre and colleagues, based on co-immunoprecipitation studies, proposed the interaction between the $\sigma_1R$ and the L-type VGCC endogenously expressed in the RGC-5 retinal ganglion cell line (Tchedre et al. 2008). At the functional level, they found that the $\sigma_1R$ agonist (+)-SKF-10047 inhibited potassium chloride-induced $Ca^{2+}$ influx in the RGC-5 cell line and $Ca^{2+}$ currents in rat cultured primary RGCs (Tchedre et al. 2008). Also in retinal ganglion cells, co-localization studies demonstrated that $\sigma_1Rs$ and L-type VGCCs co-localized and calcium imaging studies showed that $\sigma_1R$ agonists (+)-SKF10047 and (+)-pentazocine inhibited calcium ion influx through activated VGCCs (L-type). Antagonist treatment using BD1047 potentiated $Ca^{2+}$ influx through activated VGCCs and abolished inhibitory effects of the $\sigma_1R$ agonists (Mueller et al. 2013). Similar data were obtained using rat intracardiac and superior cervical ganglia neurons where sigma ligands could decrease peak $Ca^{2+}$ channel currents of N, P/Q, and R-types (Zhang and Cuevas 2002). In addition to affecting a broad population of calcium channel types, $\sigma_1R$ ligands altered the biophysical properties of these channels,

accelerating channel inactivation rate and shifting the voltage dependence of both steady-state inactivation and activation toward more negative potentials. Both $\sigma_1$R agonists and antagonists depressed $Ca^{2+}$ channel currents, with a rank order of potency (haloperidol > ibogaine > (+)-pentazocine > DTG) consistent with the effects being mediated by $\sigma_2$R and not by $\sigma_1$R (Zhang and Cuevas 2002). A similar behavior has been described in dissociated rat DRG neurons, as $\sigma_1$R agonists (+)-pentazocine and DTG inhibited $Ca^{2+}$ currents in patch-clamp experiments (Pan et al. 2014). The effect was ascribed to $\sigma_1$R activation as it was blocked by the $\sigma_1$R antagonists BD1063 or BD1047. 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 BD1063 had no effect by itself in normal non-injured DRGs, its application increased $Ca^{2+}$ currents in axotomized ones (Pan et al. 2014). Pan and colleagues already noticed these paradoxical results, as $\sigma_1$R antagonists exert antinociceptive effects while $\sigma_1$R agonists are pronociceptive, and it is also known that painful nerve injury is accompanied by reduction of $Ca^{2+}$ current in axotomized sensory neurons, which in turn results in elevated sensory neuron excitability. Similarly, it should be noted that $Ca^{2+}$ 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 DH 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 $Ca^{2+}$ 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 $\sigma_1$Rs at peripheral sites, including DRGs, may thus relieve pain by rescuing $Ca^{2+}$ currents required for natural suppression of repetitive firing via opening of calcium-activated potassium channels.

### 4.1.4 Calcium-Activated Potassium Channels

Apart from voltage-sensitive potassium channels, $\sigma_1$R has been described to regulate non-voltage-dependent, small conductance (SK) calcium-activated potassium channels (Martina et al. 2007). SK potassium channels are non-voltage-sensitive, potassium selective, and activated by an increase in intracellular $Ca^{2+}$ concentrations. SK channels activation, through the $Ca^{2+}$ increases produced after action potentials, mediates membrane hyperpolarization, which limits firing frequency of repetitive action potentials (Vergara et al. 1998). $Ca^{2+}$ entry after synaptic activation opens SK channels that act to limit the amplitude of synaptic potentials and reduce $Ca^{2+}$ influx through NMDARs (Ngo-Anh et al. 2005). It has also been established that $Ca^{2+}$ influx through NMDAR could open $Ca^{2+}$-activated $K^+$ channels in several systems. Using the $\sigma_1$R 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 (Martina et al. 2007). Moreover, the enhanced NMDAR activity was translated into an increased synaptic plasticity as evidenced by a long-term potentiation effect (Martina et al. 2007). Another study also found that DTG inhibited SK channel in midbrain dopaminergic neurons and transiently transfected HEK-293 cells, but other $\sigma_1$R 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 $\sigma_1$R antagonist BD1047, which argues against a coupling of $\sigma_1$Rs to SK channels and suggests that DTG directly blocks SK channels (Lamy et al. 2010). Thus, in the absence of further studies, it is difficult to know whether $\sigma_1$R actually regulates NMDAR via SK channels or if it is a ligand- or cell type-dependent finding.

### 4.1.5 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 (Osmakov et al. 2014). A direct interaction between $\sigma_1$R and ASIC using atomic force microscopy (AFM) in double transfected HEK cells has been described, which can be modulated by $\sigma_1$R ligands. The $\sigma_1$R antagonist haloperidol was able to reduce the ASIC1a/$\sigma_1$R binding about 50% (Carnally et al. 2010). Moreover, $\sigma_1$R/ASIC physical interaction has also functional consequences. Thus, $\sigma_1$R agonists decreased acid-induced ASIC1a currents and intracellular $Ca^{2+}$ elevations in rat cortical neurons (Herrera et al. 2008), an effect ascribed to $\sigma_1$R engagement because the inhibitory effect was counteracted by $\sigma_1$R antagonists. In contrast, in ischemic pain induced by hindlimb thrombus, the $\sigma_1$R antagonist BD1047 reduced mechanical allodynia at the periphery synergistically with the ASIC blocker amiloride, whereas the $\sigma_1$R agonist PRE-084 induced mechanical allodynia when coadministered with an acidic pH solution, thus suggesting that $\sigma_1$R activation facilitates ASICs to promote pain (Kwon et al. 2016).

### 4.1.6 Ligand-Gated Calcium Channels

Ligand-gated calcium channels such as the glutamate NMDAR also interact with $\sigma_1$R. Increased $Ca^{2+}$ influx through NMDAR and increased level of phosphorylation of these glutamate receptors have been reported following $\sigma_1$R activation (Monnet et al. 2003; Roh et al. 2008; Kim et al. 2008). This increase in the NMDAR phosphorylation state and activity is accompanied by enhanced pain behaviors. Recently, a direct physical interaction of the $\sigma_1$R with the C terminal of the NMDAR NR1 subunit has been described (Balasuriya et al. 2013; Sanchez-Blazquez et al. 2014b; Rodriguez-Munoz et al. 2015) both in vitro and in vivo using different technical approaches including bimolecular fluorescent complementation in double transfected CHO cells, in vitro pull-down assays, co-immunoprecipitation, or co-localization immunohistochemistry from PAG. This physical interaction also modulates the cross-talk between opioid analgesia and NMDAR activity (Pasternak et al. 1995; Garzon et al. 2012).

Garzon's group have shown how $\sigma_1$R antagonists are able to uncouple the $\sigma_1$R-NMDAR association while increasing opioid analgesia and reducing the development of opioid tolerance. All these evidences suggest a role of the $\sigma_1$R 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 (Sandkuhler 2000; Rygh et al. 2002).

## 4.2 G Protein-Coupled Receptors and Intracellular Second Messenger Machinery

Several G protein-coupled receptors (GPCRs), including targets clearly involved in pain modulation such as the cannabinoid $CB_1$ and μ-opioid (MOR) receptors, have been described as $\sigma_1$R partners (Kim et al. 2010; Sanchez-Blazquez et al. 2014a). $\sigma_1$R modulation of opioid receptors was initially described by Chien and Pasternak (1993, 1994) demonstrating that $\sigma_1$R 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 $\sigma_1$R 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 three- to tenfold to the left (Kim et al. 2010). A detailed review of the interaction between MOR and $\sigma_1$R is covered in another chapter of this book. 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 (Romero-Sandoval et al. 2015). Similarly to MOR, a physical interaction with $\sigma_1$R has been described for $CB_1$ receptors (Sanchez-Blazquez et al. 2014a). A functional in vivo relationship between these two receptors was demonstrated using the tail-flick test. The NMDAR increased its activity in $\sigma_1$R KO mice and it was no longer regulated by cannabinoids as in WT counterparts. Moreover, NMDAR antagonism in the $\sigma_1$R KO animals produced no effect on cannabinoid analgesia. Pharmacological intervention showed similar results, because antagonizing $\sigma_1$R prevented NMDAR antagonists from reducing CB1 receptor-induced analgesia. For both $\sigma_1$R-MOR-NMDAR and $\sigma_1$R-$CB_1$-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 (Garzon et al. 2015). A direct physical interaction between this protein and the $\sigma_1$R has been shown recently (Sanchez-Blazquez et al. 2014a) and the coordinated interaction of HINT1 and $\sigma_1$R with NMDAR and its GPCRs partners is able to control the analgesia mediated through those GPCRs. 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 (Tappe-Theodor et al. 2012). The ability of $\sigma_1$R 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. $\sigma_1R$ activation has been also shown to stimulate PLC to produce diacylglycerol (DAG) and $IP_3$ (Morin-Surun et al. 1999), which in turn leads to the activation of $IP_3$ receptors and efflux of intracellular $Ca^{2+}$ to the cytoplasm. There is growing evidence that $\sigma_1R$ is an important player at the endoplasmic reticulum (ER) regulating $Ca^{2+}$ homeostasis. In such a role, $\sigma_1R$ interacts directly with ankyrin B, BiP, or $IP_3$ receptors (Hayashi and Su 2001, 2007; Shioda et al. 2012) and ultimately regulates intracellular $Ca^{2+}$ mobilization from the ER to mitochondria in the mitochondria-associated ER membrane (MAM) (Shioda et al. 2012). $\sigma_1R$ activation leads to a diminished interaction with ankyrin and BiP, an increase in its interaction with $IP_3$ receptor, and finally a stabilization of $IP_3$ receptors, thus facilitating $Ca^{2+}$ efflux. $\sigma_1R$ agonists caused the dissociation of ankyrin B and $IP_3$ receptors and this activity correlated with the ability of these ligands to potentiate intracellular $Ca^{2+}$ mobilization induced by bradykinin. This increase in $Ca^{2+}$ could be reversed by a $\sigma_1R$ antagonist (Hayashi et al. 2000). Similarly, in CHO cells overexpressing a C terminal EYFP tagged $\sigma_1R$, agonists, such as (+)-pentazocine and PRE-084, caused very significant uncoupling of the $\sigma_1R$-BiP complex, whereas antagonists, such as NE100 or haloperidol, were not able to modify that complex at all.

## 5 Oligomerization

$\sigma_1R$ interacts with itself (Pal et al. 2007; Mishra et al. 2015). A GXXXG motif is involved in the oligomerization process, as mutations of this $\sigma_1R$ region reduced the number of receptors in higher oligomeric states and favored smaller oligomeric forms (Fig. 1) (Gromek et al. 2014). These higher order oligomers have been also demonstrated more recently by means of FRET spectrometry (Mishra et al. 2015). Moreover, only oligomeric and not the monomeric forms of $\sigma_1R$ could bind the specific agonist (+)-pentazocine. Another finding by Gromek and colleagues was that ligand binding to $\sigma_1R$ oligomers could prevent the formation of the monomer form, emphasizing the important role that $\sigma_1R$ oligomers have on its pharmacology. Thus, pharmacological activity of $\sigma_1R$ ligands, including their pro- or antinociceptive activities, could be at least in part consequence of their influence in regulating and/or interacting with $\sigma_1R$ oligomeric states. Recently, a trimeric crystal structure with agonist and antagonist bound ligands (one ligand per monomer) has been described (Schmidt et al. 2016).

## 6 Changes in $\sigma_1R$ Receptor Expression in Pain Conditions

As mentioned above, the $\sigma_1R$ is expressed in areas important for pain control such as DRG neurons, DH spinal cord, thalamus, PAG, and RVM. It is expressed by both sensory neurons and satellite cells in rat DRG (Bangaru et al. 2013). Its expression in the spinal cord is upregulated during the induction phase of neuropathic

pain following sciatic nerve constriction (Roh et al. 2008; Moon et al. 2014; Son and Kwon 2010) and in the brain 10 weeks after the induction of diabetic neuropathy (Mardon et al. 1999). Moreover, $\sigma_1$R expression significantly increased in skin, sciatic nerve, and DRG at 3 days in a model of thrombus-induced pain in rats (Kwon et al. 2016). On the contrary, $\sigma_1$R expression has been reported to be reduced in spinal cords following chemotherapy (oxaliplatin and paclitaxel) treatment (Tomohisa et al. 2015) and in axotomized neurons and accompanying satellite glial cells following spinal nerve ligation in rats (Bangaru et al. 2013). Therefore, regulation of $\sigma_1$R expression in neuropathic pain does not provide a direct explanation for pain relief after $\sigma_1$R blockade but could instead represent an adaptive counteracting mechanism.

## 7 Electrophysiological Studies

Intrinsic DH neurons receive efferent nociceptive stimuli and are also responsible for sending the nociceptive input to supraspinal structures (Almeida et al. 2004). Repetitive stimulation of the dorsal root at stimulus intensities activating nociceptive fibers, but not non-nociceptive sensory fibers, produces an amplification of the nociceptive signals in the spinal cord known as wind-up response. Wind-up is a short-term, frequency-dependent, amplification mechanism distinct from long-term potentiation, central sensitization, and pain hypersensitivity/hyperalgesia, but it is a form of homosynaptic central facilitation of nociceptive messages and a correlate of such phenomena (Dickenson and Sullivan 1987; Herrero et al. 2000). Pharmacological $\sigma_1$R antagonism modulates spinal excitability, as shown in isolated mice spinal cords superfused with the $\sigma_1$R antagonist E-52862 and stimulated electrically. E-52862 did not modify the Aβ-fiber-mediated non-nociceptive signaling and the response to single stimuli at C-fiber intensity, which is consistent with the behavioral observation that $\sigma_1$R antagonists did not alter the normal perception of sensory subthreshold and nociceptive suprathreshold inputs in non-sensitizing conditions (Cendan et al. 2005a; Entrena et al. 2009a; Romero et al. 2012). However, E-52862 dose-dependently inhibited the spinal wind-up phenomenon when repetitive stimulation of nociceptive afferent C-fibers was applied (Romero et al. 2012; Mazo et al. 2015). Accordingly, spinal wind-up amplification of the nociceptive signals was highly reduced in spinal cords from $\sigma_1$R KO compared to WT mice (de la Puente et al. 2009). Hence, electrophysiological data point to a modulatory role of $\sigma_1$R on spinal excitability, whereby pharmacological antagonism or the absence of the receptor in KO mice inhibits the amplified spinal response that would normally arise from repetitive nociceptor stimulation. Inhibition of spinal hyperexcitability could underlie the effects exerted by $\sigma_1$R antagonists on a wide variety of pain conditions in which sustained, repetitive afferent drive following injection of some chemical irritants (e.g., capsaicin and formalin), tissue injury/inflammation, or nerve damage comes to the spinal cord.

## 8 Neurochemical Studies

The spinal cord is an important gateway for peripheral pain signals transmitted to the brain. In chronic pain states, painful stimuli trigger afferent fibers in the DH to release neuropeptides and neurotransmitters, including excitatory (e.g., glutamate) and inhibitory (e.g., GABA) neurotransmitters (Thomas Cheng 2010). Modulation by $\sigma_1$R of formalin-evoked changes in neurotransmitter levels in the spinal DH was investigated using concentric microdialysis in the ipsilateral DH of awake, freely moving rats (Vidal-Torres et al. 2014). Levels of three key neurotransmitters were measured as a neurochemical correlate of three major neuronal components regulating DH neurons and accounting for spinal sensitization: glutamate for primary activating afferent inputs to the DH, GABA for local inhibitory DH interneurons, and noradrenaline for supraspinal descending inhibitory modulation of the DH. Formalin-induced nociception enhanced glutamate levels in the DH spinal cord, which is coherent with the activation of afferent glutamatergic nociceptive fibers. Systemic administration of the $\sigma_1$R antagonist E-52862 exerted antinociceptive effects on formalin-induced pain concomitantly with attenuation of formalin-evoked glutamate release and enhancement of noradrenaline levels in the spinal DH. GABA levels were not modified. These data suggest that pharmacological blockade of $\sigma_1$R reduces peripheral activating glutamatergic nociceptive inputs and enhances noradrenergic descending inhibitory inputs to the DH, but it does not modify the activity of GABAergic inhibitory DH interneurons. Interestingly, i.t. pretreatment with the alpha 2($\alpha_2$)-adrenergic receptor antagonist idazoxan prevented the systemic antinociceptive effect of E-52862, suggesting that antinociception elicited by $\sigma_1$R blockade depends on the activation of descending inhibitory pathways, which results in enhancement of noradrenaline release into the spinal cord and activation of spinal $\alpha_2$-adrenoceptors. Noradrenaline could act on presynaptic $\alpha_2$-adrenoceptors on central projections of formalin-sensitive DRGs to inhibit glutamate release to the superficial DH laminae. Glutamate is released into the DH spinal cord following activation of sensory afferents and its sustained release following sustained stimulation of nociceptors promotes plastic changes leading to spinal amplification of nociceptive messages. Thus, this excitatory amino acid plays a major role in central sensitization phenomena, including wind-up, and the behavioral manifestations of pain sensitization/hypersensitivity (D'Mello and Dickenson 2008; Latremoliere and Woolf 2009). Noradrenaline plays a major role in descending pathways that influence nociceptive signaling in the DH of the spinal cord. Descending inhibition largely involves the release of noradrenaline in the spinal cord from brainstem nuclei such as the locus coeruleus (LC), acting predominantly at the $\alpha_2$-adrenoceptors, and inhibiting transmitter release from primary afferent terminals and suppressing firing of projection neurons in the DH (Millan 2002; D'Mello and Dickenson 2008). The descending noradrenergic pathways from the brainstem to the DH may also undergo plastic changes in chronic pain states, which results in an increased inhibitory drive that has been suggested to be a homeostatic mechanism counteracting the increased spinal excitability (D'Mello and Dickenson 2008). Accordingly, the finding that E-52862 inhibited formalin-evoked glutamate but enhanced noradrenaline release in the DH (Vidal-Torres et al. 2014) is in agreement with a

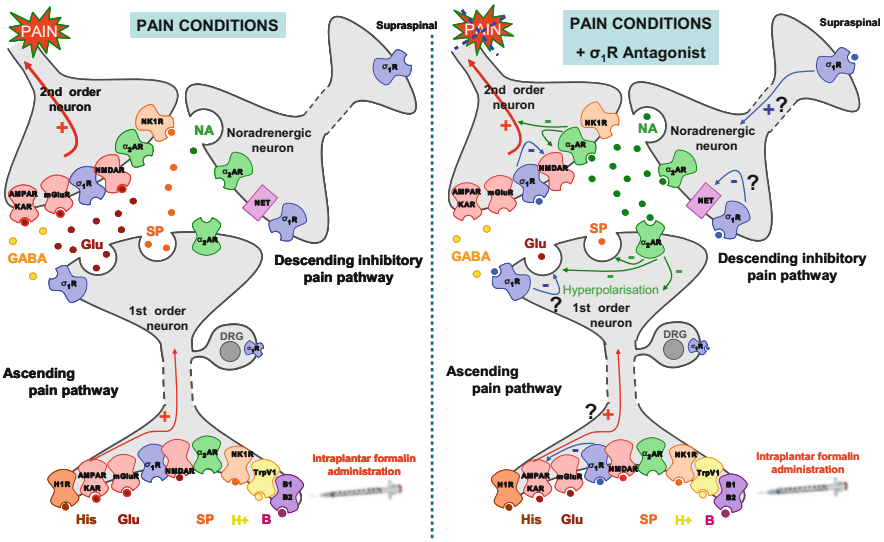


**Fig. 2** $\sigma_1$R involvement in pain modulation: neurochemistry studies in the spinal cord. Two major pathways are involved in the mechanism of action of $\sigma_1$R antagonism in the formalin-induced pain: the inhibition of the spinal excitatory synaptic transmission (Glutamate, Glu levels reduction) and the activation of descending inhibitory systems (Noradrenaline, NA levels enhancement) (Vidal-Torres et al. 2014). Regarding dorsal horn (DH) Glu levels reduction, we hypothesize that $\sigma_1$R antagonism reduces the formalin-induced increase in Glu levels by: (1) a direct $\sigma_1$R-mediated inhibition of Glu release from the central DRG endings (modulated by $\sigma_1$R located presynaptically at the DH central endings or/and postsynaptically at the peripheral endings, which would equally involve hyperpolarization of the first order neuron) or/and (2) an indirect presynaptic, NA-mediated inhibition of Glu release from central afferent endings through presynaptic $\alpha_2$-adrenoreceptors. This inhibition on Glu release would result in lower activation of NMDAR in postsynaptic second order neurons transmitting pain to upper CNS areas. Regarding DH NA levels increase, $\sigma_1$R antagonism-induced enhancement of NA levels could be a consequence of direct $\sigma_1$R-mediated: (1) direct increase of NA release at the DH, (2) NA degradation inhibition, (3) inhibition of NA reuptake (NET), or/and (4) activation of supraspinal NAergic neurons projecting to the DH. In any case, increased NA spinal levels are known to produce antinociception via: (1) activation of $\alpha_2$-adrenoreceptors located presynaptically in primary central afferents, which ultimately results in a reduction of Glu and substance P release from the central endings and (2) postsynaptic activation of $\alpha_2$-adrenoreceptors located in second order DH neurons, then hyperpolarizing DH neurons and reducing the NMDAR-induced increase of NR1 subunit phosphorylation

modulatory role of $\sigma_1$R antagonists in activity-dependent plastic changes, by promoting plasticity of descending inhibitory pathways and stopping down the plastic excitatory synaptic strengthening in the DH (Fig. 2).

## 9 Pharmacological Vs Genetic Modulation of the $\sigma_1$R in Pain: Similarities and Differences

As mentioned in the previous sections, there is plenty of evidence supporting the modulatory role of $\sigma_1$R in nociception, mainly based on the pain-attenuated phenotype of $\sigma_1$R KO mice and on the antinociceptive effect exerted by $\sigma_1$R antagonists. The focus of this section falls on analyzing similarities and differences in the antihypersensitivity profile when using genetic ($\sigma_1$R KO) and pharmacological ($\sigma_1$R antagonists) approaches. Three different scenarios have emerged (Fig. 3):

- $\sigma_1$R-KO mice develop pain similarly to WT mice and $\sigma_1$R antagonists exert no antinociceptive effect in WT mice.
- $\sigma_1$R-KO mice do not develop pain or pain is attenuated and $\sigma_1$R antagonists exert antinociceptive effect in WT mice.
- $\sigma_1$R-KO mice develop pain similarly to WT mice and $\sigma_1$R antagonists exert antinociceptive effect in WT mice.

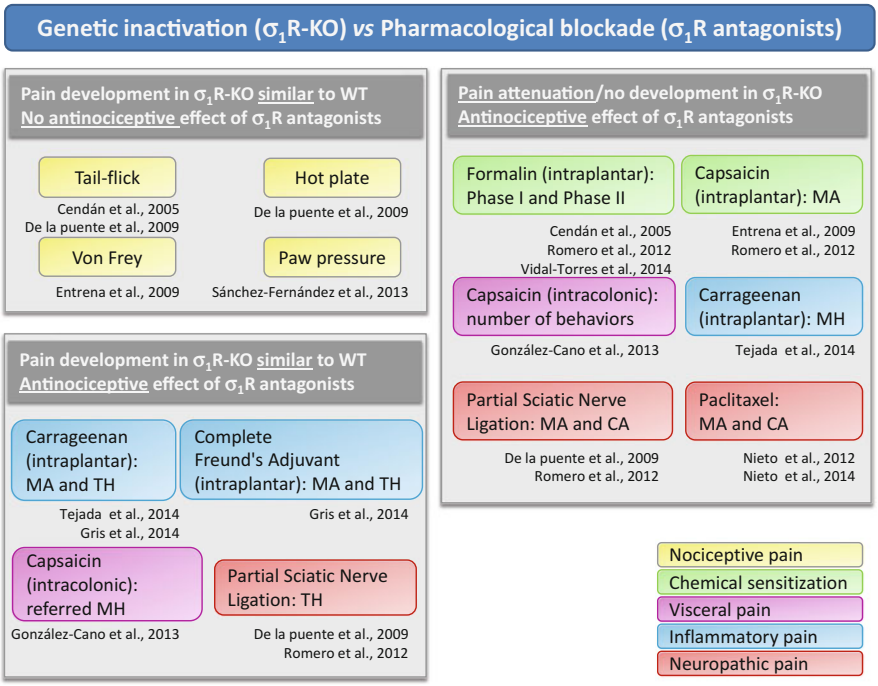


**Fig. 3** Genetic inactivation ($\sigma_1$R KO) versus pharmacological blockade ($\sigma_1$R antagonists). Similarities and differences in their impact in several pain models. *MA* mechanical allodynia, *MH* mechanical hyperalgesia, *TH* thermal hyperalgesia, *CA* cold allodynia, *KO* knockout, *WT* wild type

$\sigma_1$R KO mice are a useful genetic tool to study the involvement of $\sigma_1$R in several pain types, given that naïve KO mice perceive and respond normally to stimuli of different nature, including mechanical and thermal ones. Thus, the absence of $\sigma_1$R in KO mice has been shown to not interfere with the perception of several acute pain stimuli or with the motor response required for paw withdrawal (de la Puente et al. 2009; Entrena et al. 2009b; Nieto et al. 2012; Gonzalez-Cano et al. 2013; Sanchez-Fernandez et al. 2013; Gris et al. 2014; Tejada et al. 2014). In the same way and unlike opioid drugs, $\sigma_1$R antagonists fail to modify pain by themselves in classical models of thermal and mechanical acute nociception, as seen in the tail-flick, the hot plate, the von Frey, and the paw pressure tests in rodents (Marrazzo et al. 2006; Entrena et al. 2009a; Sanchez-Fernandez et al. 2013). $\sigma_1$R KO mice showed attenuated pain responses in both phases of the formalin test (Cendan et al. 2005b) and did not develop mechanical hypersensitivity following capsaicin sensitization (Entrena et al. 2009b). The pharmacological antagonism of $\sigma_1$R produced similar results. Accordingly, the nonselective $\sigma_1$R antagonists haloperidol and its metabolites I and II and also E-52862 inhibited formalin-induced pain (Cendan et al. 2005a; Romero et al. 2012) and somatic capsaicin-induced sensitization in mice (Entrena et al. 2009a; Romero et al. 2012).

Regarding neuropathic pain models, cold and mechanical hypersensitivity were strongly attenuated in $\sigma_1$R KO mice treated with paclitaxel (Nieto et al. 2012) or exposed to partial sciatic nerve ligation (PSNL) (de la Puente et al. 2009). However, $\sigma_1$R KO mice developed thermal hyperalgesia following PSNL (de la Puente et al. 2009). Interestingly, the pharmacological antagonism of $\sigma_1$R produced beneficial effects in all of these pain-related manifestations in WT mice. Chronic administration with $\sigma_1$R antagonists prevented the development of cold and mechanical allodynia induced by paclitaxel (BD1063 and E-52862) or PSNL (E-52862) in WT mice (Nieto et al. 2012; D'Mello and Dickenson 2008). E-52862 also prevented the development of thermal hyperalgesia induced by PSNL, although this behavior is present in the $\sigma_1$R KO mice (D'Mello and Dickenson 2008). Moreover, the acute administration of $\sigma_1$R antagonists dose-dependently reversed both paclitaxel- or PSNL-induced hypersensitivity after it had fully developed (D'Mello and Dickenson 2008; Roh et al. 2011). From a mechanistic point of view, $\sigma_1$R KO did not show increased diphosphorylated extracellular signal-regulated kinase (pERK) in the spinal cord after paclitaxel administration or PSNL (Roh et al. 2011; de la Puente et al. 2009). Thus, reduced ERK activation could contribute to the observed effects after pharmacological blockade or $\sigma_1$R genetic inactivation. In the intracolonic capsaicin visceral pain model, $\sigma_1$R KO mice have shown a reduction in the number of pain behaviors as compared to WT mice but developed referred mechanical hyperalgesia similar to WT mice (Chien and Pasternak 1995). Several $\sigma_1$R antagonists (i.e., BD1063, NE100, and E-52862) inhibited the number of behavioral responses induced by capsaicin and also reversed the referred mechanical hyperalgesia to the control threshold in WT mice (Chien and Pasternak 1995). These drugs produced no change in $\sigma_1$R KO mice, supporting a $\sigma_1$R-related mechanism for their effects.

Two different models of inflammatory pain have been explored in $\sigma_1$R KO mice, the acute inflammation induced by carrageenan and the chronic inflammation induced

by Complete Freund's Adjuvant (CFA). In the carrageenan-induced inflammatory pain model, $\sigma_1$R KO mice did not develop mechanical (paw pressure) hyperalgesia (Tejada et al. 2014) but developed mechanical (von Frey) allodynia and thermal (radiant heat) hyperalgesia (Gris et al. 2014; Tejada et al. 2014). $\sigma_1$R antagonists (i.e., BD1063 and E-52862) reversed inflammatory mechanical hyperalgesia, mechanical allodynia, and thermal hyperalgesia in WT mice, an effect which is reduced when combined with the $\sigma_1$R agonist PRE-084. However, this effect was mediated by $\sigma_1$R as BD1063 and E-52862 had no effect on thermal hyperalgesia and mechanical allodynia in $\sigma_1$R KO mice (Gris et al. 2014; Tejada et al. 2014). The antiedematous effects do not account for the decreased hyperalgesia, since carrageenan-induced edema was unaffected in $\sigma_1$R KO or by systemic $\sigma_1$R pharmacological antagonism (Tejada et al. 2014; Gris et al. 2014). Like in carrageenan-induced inflammatory pain model, the genetic inactivation of $\sigma_1$R failed to prevent the development of CFA-induced mechanical allodynia (von Frey filaments). However, the $\sigma_1$R antagonist E-52862 reversed CFA-induced mechanical allodynia only in WT mice, but not in KO mice, supporting an on-target mechanism for the effects of this drug (Gris et al. 2014).

Taken together, these data indicated that the lack of $\sigma_1$R clearly impacts on the development of neuropathic pain but it did not impact on acute nociceptive pain and partially on the development of inflammatory or visceral pain. Because nociceptive, neuropathic, visceral, and inflammatory pains are known to involve different pathways, the different phenotypes observed in $\sigma_1$R KO mice suggest, depending on the pain model and the readout, a different involvement of the $\sigma_1$R system in the mechanisms underlying hypersensitivity (Gris et al. 2015). In contrast, systemically administered $\sigma_1$R antagonists provided efficacy in all pain-related behaviors evaluated in WT mice (except in acute nociceptive pain), including those developed by $\sigma_1$R KO mice (i.e., mechanical allodynia and thermal hyperalgesia induced by carrageenan, mechanical allodynia induced by CFA, referred mechanical hyperalgesia induced by intracolonic capsaicin, and thermal hyperalgesia induced by PSNL) (Fig. 3). This fact brings out the difference between the effect of genetics (i.e., the absence of the receptor and associated adaptive changes) and the pharmacological blockade of $\sigma_1$R (i.e., the modulatory effect of a ligand at the time of the test) (Gris et al. 2015; Zamanillo et al. 2013).

Several possible explanations may account for the different analgesic effect profiles generated by genetic and pharmacological approaches. First, some of the differences could be attributed to the lack of selectivity of many of the $\sigma_1$R antagonists used in the literature, in contrast to the complete and specific inhibition in $\sigma_1$R KO. In fact, many compounds of very different structural classes and with different therapeutic applications, such as antipsychotics (e.g., haloperidol and chlorpromazine), antidepressants (e.g., fluvoxamine, sertraline, and clorgyline), antitussives (carbetapentane, dextromethorphan, and dimemorfan), drugs for the treatment of neurodegenerative disorders such as Parkinson's disease (amantadine) or Alzheimer's disease (memantine and donepezil), and drugs of abuse (cocaine and methamphetamine) can bind, with high to moderate/weak affinity and with no selectivity, to $\sigma_1$R and some of them have been used (e.g., haloperidol) to characterize $\sigma_1$R pharmacology (Zamanillo et al. 2013; Almansa and Vela 2014). Other compounds (e.g., panamesine, rimcazole, eliprodil,

and others) have been developed as $\sigma_1$R ligands, but their selectivity against $\sigma_2$R and/or other targets is far from optimal. However, the lack of selectivity cannot be longer supported as an explanation considering results coming from selective compounds such as E-52862. E-52862 shows high affinity for $\sigma_1$R (Ki = 17 nM) and a good $\sigma_1$R/$\sigma_2$R selectivity ratio (>500). Moreover, it is selective over a panel of 170 molecular targets. It behaves as an antagonist, penetrates the blood–brain barrier, and binds to $\sigma_1$R in the CNS. Occupancy of $\sigma_1$R in the CNS by E-52862 significantly correlated with its antinociceptive effects (Romero et al. 2012). The use of E-52862 as a highly selective $\sigma_1$R antagonist has provided a good pharmacological tool to really assess the role of $\sigma_1$R in pain modulation. Furthermore, and even more convincing, its activity disappears when administered to $\sigma_1$R KO mice.

A second possible explanation is that, unlike the pharmacological treatment in WT mice which produces temporary blockade of $\sigma_1$R, $\sigma_1$R KO mice are completely deficient in $\sigma_1$R function throughout development and adult life. We therefore speculate that pain-related behaviors developed in $\sigma_1$R KO mice may be related to the developmental effects of global $\sigma_1$R deletion and this cannot be mimicked by treating with antagonists to adult WT mice. Although our initial characterization of $\sigma_1$R KO mice did not reveal any overt phenotype, compared with their WT litter mates (Langa et al. 2003), some subtle changes at the level of gene expression may exist throughout life, leading to altered neuroadaptation. This notion of a unique, early development effect by the genetic KO approach has been suggested to account for the discrepancy between genetic KO and pharmacological blockade approaches (Gingrich and Hen 2000). Thus, some effects may not be due to the absence of the receptor in the adult mouse but to the lack of the receptor at some earlier point in development. This has been shown for serotonin 5-$HT_{1A}$ receptors. A developmentally controlled rescue strategy showed that postnatal developmental expression of 5-$HT_{1A}$ receptors is important to establish anxiety-like behavior in adult mice (Gross et al. 2002). In addition, there are studies reporting compensatory effects and conflicting results between pharmacological and genetic inactivation in different cases such as the role of adenosine $A_{2A}$ receptors in psychostimulant-induced behavioral responses and gene expression profiles (Chen et al. 2000, 2003; Yu et al. 2005), the role of 5-$HT_7$ receptors in depression (Guscott et al. 2005), GABAergic modulation of seizure activity (Voss et al. 2010), endocannabinoid signaling (Min et al. 2010), and the role of δ-subunit-containing γ-aminobutyric acid subtype A receptors in nociception (Bonin et al. 2011), among others. Conditional/inducible mutation approaches, that first allow the mouse to develop and mature normally prior to ablation of the gene of interest, could be of interest to understand discrepancies noted between pharmacological and genetic inactivation.

A third possibility arises from the chaperone nature of $\sigma_1$R, which exert their action by physical protein–protein interactions. Accordingly, the absence of the regulatory mechanism in KO mice is not equivalent to the decrease or gain of function promoted by a $\sigma_1$R ligand through conformational changes relating to and affecting the activity of the target protein with which $\sigma_1$R interacts. In other words, the absence of the modulatory system, as in KO mice, precludes the regulation by ligands, but it does not mimic the modulatory effect elicited by a $\sigma_1$R ligand.

## 10 Concluding Remarks

The effects reported with $\sigma_1$R ligands (pronociceptive in the case of agonists and antinociceptive in the case of antagonists) are consistent with a role for $\sigma_1$R in central sensitization and pain hypersensitivity and suggest a potential therapeutic use of $\sigma_1$R antagonists for the management of neuropathic pain and other pain conditions including inflammatory, visceral, ischemic, postoperative, and orofacial pain. The $\sigma_1$R acts as a modulator of the intracellular signaling incurred upon activation of several receptors, enzymes, and ion channels relevant in pain transmission and processing, but the $\sigma_1$R is devoid of its own specific signaling machinery. Ligands acting on $\sigma_1$R can amplify or reduce the signaling initiated when the target protein that the $\sigma_1$R is interacting with becomes activated, but they are per se inactive. On this basis, $\sigma_1$R 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, $\sigma_1$R ligands exert their modulatory activity under conditions involving a disturbance, such as chronic pain. In other words, under normal physiological conditions most target proteins are not affected by $\sigma_1$R ligands. 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 $\sigma_1$R antagonists, no adverse events have been described in rodents at doses exerting antinociceptive effects based on preclinical studies. Unlike other analgesics (e.g., opioids), $\sigma_1$R antagonists do not modify the normal sensory perception, and normal/baseline nociceptive thresholds are not modified when $\sigma_1$R 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), a $\sigma_1$R antagonist can exert its effect, which is the reversion of the diminished pain thresholds back to normal sensitivity thresholds. Accordingly, $\sigma_1$R antagonists are not strictly analgesics; they are antiallodynic and antihyperalgesic drugs. Moreover, there is plenty of data supporting the combination of $\sigma_1$R antagonists with opioid therapy, which may result in a potentiation of opioid analgesia without significant increase in unwanted effects. These observations mean that lower doses of opioids, with less side effects but efficacious based on the selective enhancement of the analgesic effect, could be potentially used if $\sigma_1$R antagonists are used as opioid adjuvants.

Overall, based on the preclinical data, the use of selective $\sigma_1$R antagonists could represent a promising efficacious and safe strategy to approach difficult-to-treat chronic pain conditions including neuropathic pain, and to enhance analgesic efficacy and increase the safety margin of opioids. In this regard, the most advanced investigational $\sigma_1$R antagonist, E-52862, exhibited an acceptable safety, tolerability, pharmacodynamic, and pharmacokinetic profile in phase I studies and is now in phase II studies in chronic neuropathic pain and in postoperative pain in combination with morphine. The outcome of clinical studies with the $\sigma_1$R antagonist E-52862 will be of great interest to assess the potential of this new therapeutic approach to pain management.

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