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The molecular function of σ receptors: past, present, and future

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Abstract

The σ_1 and σ_2 receptors are enigmatic proteins that have attracted attention for decades due to the chemical diversity and therapeutic potential of their ligands. However, despite ongoing clinical trials with σ receptor ligands for multiple conditions, relatively little is known regarding the molecular function of these receptors. In this review, we revisit past research on σ receptors, and discuss the interpretation of these data in light of recent developments. We provide a synthesis of emerging structural and genetic data on the σ_1 receptor and discuss the recent cloning of the σ_2 receptor. Finally, we discuss the major questions that remain in the study of σ receptors.

Keywords

σ_1 receptor; σ_2 receptor/TMEM97; structural pharmacology; molecular pharmacology

The σ receptors: enigmatic therapeutic targets

The σ_1 and σ_2 receptors have been the subject of intense study by pharmacologists for over four decades [1, 2]. Both receptors have been proposed as therapeutic targets for several diseases and conditions. The σ_1 receptor is considered a potential therapeutic target for pain management [3] and neurological pathologies such as amyotrophic lateral sclerosis (ALS) [4, 5], Alzheimer's disease [4, 5], Parkinson's disease [4, 5], retinal disease [6], stroke [4], and cocaine [7] and alcohol [8] addiction. Additionally, there is interest in using σ_1 and σ_2 receptor ligands for treating [9, 10] and imaging [11] cancer. Currently, σ_1 receptor ligands are in clinical trials for the treatment of chemotherapy-induced neuropathic pain [12], Alzheimer's disease [13], and ischemic stroke [14]. Meanwhile, one σ_2 receptor ligand recently showed efficacy against the negative symptoms of schizophrenia in a phase II clinical trial [15], and another was well tolerated in a phase I clinical trial for Alzheimer's disease and is now entering phase II [16].

Despite intense therapeutic interest, many of the molecular details of both σ_1 and σ_2 receptor functions remain unclear. The last five years have seen considerable progress in σ receptor genetics, structural biology, and biochemistry, but major questions remain

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unanswered. In this review we discuss recent advances in σ receptor molecular biology and biochemistry and consider both how these advances inform our interpretation of previous work and what major challenges lie ahead.

Discovery and molecular pharmacology of the σ receptors

In 1976, pharmacological studies of opioids and opioid-like compounds in dogs led to the proposal of three distinct opioid receptor subtypes: μ, κ, and σ [1]. However, radioligand binding experiments quickly revealed that the σ receptor binding site was distinct from the opioid receptors [1]. Specifically, the σ receptor does not bind to classical opioid ligands such as naloxone, etorphine, or (–) benzomorphans [1]. Instead, the σ receptor has high affinity for (+) benzomorphans [1] in addition to myriad small molecules that exhibit little structural similarity to one another [1] (Figure 1). The receptor's unusual pharmacological profile attracted interest from pharmacologists throughout the 1980s and 1990s. However, the receptor's promiscuous ligand binding profile meant that few selective ligands existed, complicating efforts to unambiguously ascribe pharmacological effects to it. This difficulty was overcome with the development of [^{3}H](+)-pentazocine, a radioligand with high affinity and specificity for the σ_1 receptor [17].

The use of [^{3}H](+)-pentazocine enabled two major advances in σ receptor pharmacology. The first was the identification of two distinct σ receptor binding sites [18]. The first site was dubbed σ_1 and largely corresponds to the classical σ receptor defined by Su and Tam [1] described above. The second site was named σ_2, and like σ_1 it exhibits high affinity for both ditolylguanidine (DTG) and haloperidol. However, the σ_2 receptor does not bind benzomorphans [18]. The second major advance enabled by [^{3}H](+)-pentazocine was the identification of a minimal **pharmacophore (see Glossary)** sufficient for high-affinity binding to the σ_1 receptor. This simple pharmacophore features a single positively charged nitrogen flanked by two hydrophobic or aromatic moieties 6 – 10 Å and 2.5 – 3.9 Å in length [19] (Figure 1). All known σ_1 receptor ligands with high affinity (K_D < 50 nM) fit this model [19].

No endogenous ligand has been definitively identified for σ receptors. Early work demonstrated that the σ_1 receptor has affinity for some steroids, especially progesterone [1]. However, physiological concentrations of progesterone are thought to be low relative to its K_d for the σ_1 receptor [20], and though the σ_1 receptor is sometimes localized to the plasma membrane, it is primarily an intracellular receptor [21]. However, pharmacological manipulation of steroid synthesis can alter the accessibility of σ_1 receptor sites in the brain [22]. Similarly, others have proposed that the hallucinogen *N*,*N*-dimethyltryptamine (DMT) is an endogenous ligand for the σ receptor [23], but DMT has only a 14.75 μM affinity for the σ_1 receptor, while its plasma concentrations are not thought to exceed 500 nM, making it unlikely that this interaction is physiological [24]. Additionally, other work has shown that DMT has much higher affinity for 5-HT receptors, which are probably responsible for its hallucinogenic effects [25]. D-erythro-sphingosine has also been proposed as an endogenous σ_1 receptor ligand, though the affinity for the receptor was variable depending on the assay used [26], and it has not been demonstrated that the interaction occurs in living cells. A

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recent paper suggested that choline may serve as an endogenous ligand for the σ_1 receptor [27], raising another possibility.

Molecular function of the σ_1 receptor

Despite over 40 years of study, there is still much to be learned about the molecular role of the σ_1 receptor in cells. A prevailing model is that the σ_1 receptor modulates other cellular signaling pathways by acting as a ligand-operated chaperone. Ligands of the σ_1 receptor have historically been classified as **agonists** or **antagonists** based on their ability to recapitulate the effects of genetic knockout or knockdown of the σ_1 receptor, typically in animal models [4]. Ligands that mimic σ_1 receptor genetic knockout are considered antagonists, while ligands that exert some σ_1-dependent effect distinct from genetic knockout are considered agonists [4]. A central challenge in functional studies of the σ_1 receptor is its lack of similarity to other human proteins. The σ_1 receptor was cloned in 1996 [28], and while the σ_1 receptor is conserved among vertebrates, it bears no similarity to any other mammalian protein. Its closest homolog is the yeast **C8-C7 sterol isomerase**, ERG2p [28]. However, the σ_1 receptor itself has no sterol isomerase activity [28].

The σ_1 receptor as a modulator of cellular signaling

In general, the σ_1 receptor is thought of as a modulator of other signaling pathways, particularly **G protein-coupled receptor (GPCR)** and **ion channel** signaling. Throughout the 1980s and 1990s, evidence suggested that the σ_1 receptor may be involved in intracellular calcium signaling and **inositol triphosphate (IP_3)** turnover [1, 29–32]. In 2001, Hayashi and Su used **co-immunoprecipitation (Co-IP)** experiments to suggest that at least some these effects were mediated through a complex of σ_1 receptor, IP_3 receptor, and ankyrin B [33] (Table 1). The next year, Aydar et al. showed that σ_1 receptor activation could inhibit potassium channels in *Xenopus* oocytes and that the σ_1 receptor could Co-IP with $K_V1.4$ [34]. These two studies precipitated a shift in the way σ_1 receptor was thought to modulate other signaling pathways. Over the last two decades, the σ_1 receptor has been shown to influence the cellular function of many proteins, and the proposed mechanism for this modulation has often been direct σ_1 receptor-protein interactions (Table 1). To date, the σ_1 receptor has been reported to bind to at least 49 proteins, many of which are highly divergent in sequence and structure (Table 1).

While the modulation of ion channel [31, 34–39] and GPCR [40–45] signaling by σ_1 receptor ligands is relatively well established, more work is needed to determine if these modulatory effects result from direct σ_1-protein interactions. Multiple reports have shown instances where σ ligands directly modulate ion channels independently of the σ_1 receptor [46–49], and many of the reported effects of σ ligands on ion channels require concentrations of 10 μM or more despite nanomolar affinity for the receptor [31, 50–56]. Additionally, evidence for direct σ_1-protein interactions have relied primarily on Co-IP, **resonance energy transfer (RET)**, or **proximity ligation** experiments (Table 1). These methods demonstrate proximity but cannot distinguish between direct and indirect interactions. Additionally, while Co-IP experiments can be informative, Co-IPs between membrane proteins are prone to false positives due to incomplete membrane solubilization

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and protein aggregation. Thus, it is desirable to validate molecular interactions suggested by such experiments with methods that can demonstrate direct molecular interactions. Ideally, these interactions are cross-validated with reconstituted biochemical or biophysical assays. **Atomic force microscopy (AFM)** has been used to investigate the properties of several σ_1 receptor-ion channel complexes [36, 37, 57, 58], but this technique lacks sufficient resolution to show that the proteins are interacting in a specific manner with physiologically relevant affinities. Altogether, more work is needed to understand the mechanism of σ_1 receptor modulation of GPCRs, ion channels, and other proteins.

The σ_1 receptor as a ligand-operated chaperone

The identification of a large number of protein-protein interactions between the σ_1 receptor and other proteins is consistent with the possibility that the σ_1 receptor is a ligand-operated **chaperone**. This idea was first proposed by Hayashi and Su [21] and has since become a prevailing model in the field [2, 4–6]. In this model (Figure 2), the σ_1 receptor exists in a resting state at the **mitochondrion-associated membrane (MAM)** of the endoplasmic reticulum (ER) [5]. While at the MAM, the σ_1 receptor forms a complex with a chaperone called the binding immunoglobulin protein (BiP), which plays a central role in protein folding and quality control [5]. Activation of the σ_1 receptor by small molecule agonists or by a decrease in ER calcium concentrations cause the σ_1 receptor to dissociate from BiP and interact with client proteins in the ER or other organelles [2, 5] (Table 1; Figure 2).

Though this model is widely accepted [2, 4–6], direct evidence for the receptor's chaperone activity is relatively limited. To date, only one reconstituted biochemical experiment to demonstrate chaperone activity by the σ_1 receptor has been published [21]. In this experiment, the authors monitored the ability of a purified C-terminal fragment of the σ_1 receptor (residues 116–223; Figure 3A) to minimize the aggregation of proteins in a light scattering assay. While the C-terminal fragment of the receptor did reduce light scattering [21], recent structural work makes it unclear if this fragment fully recapitulates σ_1 receptor function (see "Lessons from σ_1 receptor crystal structures").

Additional indirect evidence for the σ_1 receptor's chaperone function has been reported. For example, overexpression of the σ_1 receptor can increase the whole-cell or surface expression of various proteins [38, 59–62]. Similarly, **siRNA knockdown** of the σ_1 receptor can decrease [21, 35, 60, 63] or increase [64] the expression of other proteins. Finally, σ_1 overexpression or agonist treatment can protect cells against various forms of ER stress, while knockdown or antagonist treatment can make cells more vulnerable [21]. While these results are consistent with the idea that the σ_1 receptor could be a chaperone protein, there are other possible explanations for this activity.

For example, while the σ_1 receptor could be modulating signaling pathways through interactions with many proteins, it may also affect multiple pathways through only a subset of these interactions. The σ_1 receptor has been shown to modulate the ER stress response and subsequent **unfolded protein response (UPR)**, which can influence protein stability and localization [65, 66], presumably through binding and modulating the ER stress response regulatory protein IRE1 [63, 67]. A recent study demonstrated that the σ_1 receptor regulates IRE1 activity *in vivo*, with σ_1 receptor knockout enhancing IRE1 activation and

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the resulting inflammatory response in lipopolysaccharide-induced inflammation models [67]. Additionally, previous work suggests that the σ_1 receptor is localized to cholesterol-rich lipid microdomains [68], where it can influence the distribution of lipids in the ER [68]. Changes in ER lipid composition are strongly associated with the ER stress response and the UPR [66]. By serving as a regulator of ER stress, the σ_1 receptor could influence the signaling of many cellular pathways without needing to physically associate with more than a small number of proteins. Therefore, while the chaperone model of σ_1 receptor function may be accurate, there is not yet sufficient data to rule out alternative models of σ_1 receptor function.

σ_1 receptor oligomerization

The most well-validated σ_1 receptor protein-protein interaction is its association with itself. The formation of functional σ_1 receptor oligomers was first suggested by BRET experiments performed in HEK 293T cells [43]. This was confirmed with a careful biochemical analysis, which showed that purified σ_1 receptor existed in at least two different oligomeric states [69]. Later work in cells using both resonance energy transfer techniques [61, 70, 71] and native gels [61] has shown that the σ_1 receptor exists in multiple oligomeric states and that ligands alter the distribution of these states. Antagonists bias the receptor towards higher molecular weight states, while agonists bias the receptor towards lower molecular weight states [61, 70, 71]. The precise functional consequences of σ_1 receptor oligomerization remain to be determined.

Lessons from σ_1 receptor crystal structures

In the last three years, crystal structures of the σ_1 receptor have been solved in complex with five different ligands: PD 144418, haloperidol, NE-100, 4-IBP, and (+)-pentazocine [72, 73]. The receptor has five α helices including one transmembrane domain, and ten β strands, which make up the ligand binding domain (Figures 3A, 3B). Helices α4 and α5 are amphipathic helices that are partially embedded in the membrane. In all structures the receptor has crystallized as a homotrimer with an extensive inter-subunit interface (Figure 3B).

These structures have recast our perception of this protein's fundamental architecture. First, these crystal structures have definitively established the σ_1 receptor as a single-pass transmembrane protein (Figure 3B). Prior to this work, both single-pass and two-pass transmembrane models had been proposed for the σ_1 receptor, though the two-pass model was most often discussed [34, 74]. However, crystal structures show that the receptor has a single transmembrane domain spanning residues 9–30 [72], and later proximity labeling [75] and BRET [71] experiments have corroborated these findings in cells.

Prior to the first reported crystal structures of the σ_1 receptor, a nuclear magnetic resonance (NMR) study investigated the location of a putative second transmembrane domain of the receptor using a construct in which the first transmembrane domain had been removed [74]. In this study, the authors titrated lipid into their detergent mixture, and identified residues in the protein whose chemical shift values changed upon the addition of lipid [74]. The region comprising residues 91–107 was most sensitive to lipid titration and was tentatively

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identified as a second transmembrane domain based on the *a priori* assumption that such a domain exists [74]. However, in the crystal structure residues 91–107 form a buried hydrophobic β hairpin. Given the high hydrophobicity of this region it is not entirely surprising that it interacts with lipid, and this effect (rather than the existence of a second transmembrane domain) likely accounts for the results of this experiment.

As in the NMR studies, many other investigations have relied on the assumption of two transmembrane architecture to guide experimental design. These studies have often employed constructs lacking the N-terminal half of the protein based on the two-transmembrane model [21, 63, 76, 77]. While early work suggested that this construct may share some cellular functions with the native receptor [21, 77], the crystal structure shows that this truncation would remove the protein's first three α helices and first four β strands, which make up about half of the ligand binding domain (Figures 3A, 3C and 3D). This brings the stability and functionality of this construct into question. Thus, it can be difficult to interpret work done using constructs based on the previous models of the σ_1 receptor.

The recent structures reveal how the σ_1 receptor is able to bind many structurally diverse ligands with high affinity [1]. The σ_1 receptor interacts with most of its ligands through only a single electrostatic interaction between Glu172 and the basic nitrogen present in most σ_1 receptor ligands (Figure 3E). In all five existing crystal structures, the rest of the ligand is free to fit into the large β-barrel-like binding pocket, which is lined with hydrophobic residues. Thus, as long as the ligand is chemically and sterically suited to the ligand binding pocket's hydrophobicity and able to make the electrostatic interaction with Glu172, then the ligand may bind with high affinity. It should be noted that the σ_1 receptor has also been shown to bind some neurosteroids, which do not have a basic nitrogen atom [1]. Presumably, these ligands would interact with the receptor differently, perhaps under conditions where Glu172 is protonated. However, the relatively modest affinity of neurosteroids for the σ_1 receptor (200 nM or weaker) [1] has thus far prevented crystallization of a σ_1-steroid complex.

With the crystal structure of the σ_1 receptor bound to (+)-pentazocine [73], we also have the first glimpse as to how agonists and antagonists may differ at the structural level. The agonist (+)-pentazocine binds the receptor in the same binding pocket as antagonists, but it occupies a distinct region of this pocket from the four antagonist ligands co-crystallized with the receptor. This seems to induce a small conformational change in helix α4 that could explain why these ligands may bias the receptor towards smaller molecular weight states (Figures 3F, 3G). More work is required to see if this conformational change is caused by all σ_1 receptor agonists, and to confirm if it indeed underlies the regulation of σ_1 oligomerization.

Human genetics of the σ_1 receptor

Ten pathogenic mutations in the human σ_1 receptor gene have been reported in cohort studies (Table 2). In general, these appear to be loss of function mutations, resulting in either a form of juvenile-onset ALS known as ALS16 [78–80], a form of distal hereditary motor neuropathy (dHMN) [81–84], or other similar motor neuron deficits such as frontotemporal

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lobar degeneration with motor neuron disease (FTLD-MND) [85] or Silver syndrome (SS) [83]. These conditions feature gradual loss of motor neuron function, typically beginning in early childhood or adolescence. Mutations have been discovered in all four SIGMAR1 exons, as well as the 3' untranslated region (3' UTR) (Table 2). Though the molecular mechanism of pathogenicity is not known for all of these mutations, those mutants that have been studied often exhibit misfolding or mislocalization of the protein, resulting in cellular pathologies in the ER (Table 2).

σ_1 receptor genetics and protein structure

The recent structures of the σ_1 receptor offer an opportunity to structurally interpret the σ_1 receptor mutations reported to cause human disease. Of the ten reported pathogenic mutations, four of them delete large sections of the receptor or introduce a premature frameshift or stop codon, and two are mutations in the SIGMAR1 gene's 3' UTR (Table 2). The other four mutations each substitute a single amino acid in the mature protein (Table 2). These pathogenic mutations are L65Q, E102Q, E138Q, and E150K (Table 2, Figure 4).

The σ_1 receptor crystal structure provides a molecular rationale as to why these mutations could result in a nonfunctional receptor. The L65Q substitution would introduce a hydrophilic headgroup in a hydrophobic region of the receptor, which would be energetically unfavorable (Figure 4A). The substitutions E102Q, E138Q, and E150K would disrupt either intramolecular hydrogen bonds presumably necessary for proper folding of the receptor (E102Q and E150K, Figures 4B and 4D), or a hydrogen bonding network at the receptor's oligomeric interface (E138Q, Figure 4C).

The σ_2 receptor

In contrast to the σ_1 receptor, relatively much less is known regarding the biological roles of the σ_2 receptor. The σ_2 receptor was discovered in 1990 through pharmacological profiling of cancer cell lines, and was defined as a binding site with high affinity for DTG and haloperidol but not benzomorphans [18]. Since then, the receptor has attracted considerable interest as a therapeutic target for the treatment of cancer [9, 11] and neurologic disease [15, 16]. Pharmacological experiments showed that the σ_2 receptor is a 18 – 22 kDa intracellular membrane protein [18], and genetic knockout of the σ_1 receptor revealed that the σ_2 receptor was derived from a completely different gene than σ_1. However, the gene that codes for the σ_2 receptor was not known until very recently [86] (see "Molecular cloning of the σ_2 receptor"). This was a major impediment to studying the biological function of the σ_2 receptor, and as a result our understanding of its function is limited relative to that of other pharmacologically characterized receptors.

Molecular cloning of the σ_2 receptor

The σ_1 receptor was cloned in 1996 [28], but the gene that codes for the σ_2 receptor eluded discovery despite multiple attempts to identify it [87, 88]. The most prominent attempt suggested that the σ_2 receptor may be identical to the membrane-associated progesterone receptor membrane component 1 (PGRMC1) [88], but later work demonstrated that

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respective siRNA knockdown [89] and CRISPR knockout [90] of the murine and human PGRMC1 genes have no effect on σ_2 binding in cells.

The σ_2 receptor was finally identified as TMEM97 in 2017 [86]. This was determined via a an affinity chromatography approach in which a σ_2-specific ligand fixed to a column was used to isolate candidate proteins from calf liver [86]. Candidates were identified by mass spectrometry and screened through heterologous expression and pharmacological profiling [86]. Expression of TMEM97 in cells lacking σ_2 receptor confers a σ_2 receptor binding profile to those cells, and siRNA knockdown of TMEM97 proportionally reduces σ_2 binding [86], confirming that TMEM97 and the σ_2 receptor are one and the same.

TMEM97/σ_2 receptor biology and therapeutic potential

Currently, little is known about TMEM97 except that it resides in the endoplasmic reticulum and lysosomes [91], where it may bind to cholesterol [91] and regulate the Niemann-Pick protein NPC1 [92]. It is also overexpressed in some cancers [93–95], which had also been reported for σ_2 receptor before its identification [9].

Interest in the σ_2 receptor/TMEM97 has centered around its role as a potential therapeutic target for the diagnosis and treatment of cancer [9], as well as the treatment of schizophrenia [15] and Alzheimer's disease [16]. However, the lack of a gene for σ_2 has prevented research that could unambiguously determine if the observed effects of σ_2 receptor ligands are truly σ_2-mediated, as it was impossible to knock down or overexpress the receptor. This is poised to change now that the receptor has been cloned. Already, one report has shown that some ligands that were thought to kill cancer cells through σ_2 receptor in fact work through a σ_2-independent mechanism [96].

Evolutionary connection between the σ_1 and σ_2 receptors

The σ_1 receptor and the σ_2 receptor/TMEM97 are not genetically related to one another, but they are both related to enzymes that perform the same function. The σ_1 receptor's closest relative is the yeast C8-C7 sterol isomerase ERG2p [28]. Similarly, the σ_2 receptor/TMEM97 is related to emopamil binding protein (EBP), which is the mammalian C8-C7 sterol isomerase [97]. EBP and σ_2 receptor/TMEM97 belong to the Expanded EBP superfamily (EXPERA), a small group of 5 proteins also including transmembrane 6 superfamily members 1 and 2 (TM6SF1 and TM6SF2), and Emopamil binding protein-like (EPBL) [98]. Thus, though σ_1 and σ_2 receptors are not genetically related, their similar pharmacological profiles are likely a consequence of convergent evolution.

Indeed, despite the fact that σ_1 receptor and ERG2p are genetically dissimilar to EBP, all three proteins share similar pharmacological profiles [99]. Moebius et al. performed a detailed analysis comparing the pharmacological profiles of guinea pig σ_1 receptor, ERG2p, and EBP from guinea pig, human, and mouse [99]. They found that all three proteins could bind several σ ligands with high affinity [99]. This raises the possibility that other EXPERA domain proteins may be tractable pharmacological targets. Currently, the functions of the σ_2 receptor/TMEM97, TM6SF1, TM6SF2, and EBPL are not well understood, but it is possible

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that some or all of these proteins contribute to the physiological and behavioral effects reported for σ ligands.

Concluding remarks and future perspectives

The last five years have witnessed significant advances in our understanding of σ receptors. Crystal structures of the σ_1 receptor [72, 73] provide a rationale for the receptor's pharmacology and facilitate precise design of mutants and truncations for functional studies [27, 45, 61, 75]. Similarly, the identification of the σ_2 receptor as TMEM97 will enable the use of modern molecular biological techniques in its study. However, a great deal of work remains if we are to understand even the basic biology of σ receptors (see Outstanding questions). Moving forward, σ receptor research must build on what has been done over the last 40 years while simultaneously assessing past work with a critical eye. Prevailing ideas should be revisited with newly developed tools to provide validation and mechanistic detail that is currently unavailable. New technologies such as **CRISPR-Cas9** gene editing will help to clearly define which cellular effects of σ ligands are directly mediated by σ receptors. Though much remains to be done, this is an exciting time in σ receptor research, as our understanding of both receptors enters the molecular era.

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Glossary

Agonist
A ligand that activates a receptor to elicit a biological signaling response

Antagonist
A ligand that inactivates a receptor to prevent or attenuate a biological signaling response

Atomic force microscopy (AFM)
A form of scanning probe microscopy that uses a physical probe to scan a surface, providing an image with sub-nanometer resolution

C8-C7 sterol isomerase
An enzyme involved in the synthesis of cholesterol/ergosterol. It moves a double bond between carbons C9 and C8 to C8 and C7

Chaperone
A class of protein that assists in the folding of other proteins. Many are essential parts of the cell's protein synthesis machinery

Co-immunoprecipitation (Co-IP)
A technique in which an antibody against a "bait" protein attached to beads is used to remove the bait, and any proteins associated with it, from solution

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CRISPR-Cas9

A gene editing system that uses the enzyme Cas9 with an associated guide RNA molecule to make modifications to specific regions of an organism's DNA

G protein-coupled receptor (GPCR)

A member of a diverse family of seven-pass transmembrane receptor that couples to G proteins to transmit a biological signal

Inositol triphosphate (IP_3)

A small molecule second messenger that activates the IP_3 receptor, triggering calcium release from the ER

ion channel

A transmembrane protein that, when activated, allows specific ions to flow along their concentration gradient from one side of a membrane to another

Mitochondrion-associated membrane (MAM)

A specialized region of the ER membrane that forms a contact with the mitochondrial membrane, thought to be important for the control of calcium homeostasis, lipid metabolism, and autophagy

Pharmacophore

The part of a chemical structure that is responsible its specific interactions

Proximity ligation

A technique used to show that two proteins are within close proximity to one another. Cells are stained with primary antibodies against the proteins of interest. Secondary antibodies with complementary oligos are then added to bind to the primary antibodies. If the secondary antibodies are in close proximity, the oligos will anneal. Enzymes are added to initiate rolling DNA synthesis

Resonance energy transfer (RET)

A class of techniques used to show that two light-sensitive molecules are in close proximity to one another. A light-sensitive molecule is excited at a wavelength specific to that molecule. The excited molecule emits a photon at a wavelength that will excite the other light-sensitive molecule if the two are within close spatial proximity

siRNA knockdown

An RNA interference method that uses a short interfering RNA (siRNA) of 20–25 bp to reduce expression of the target gene through the RISC pathway

Unfolded protein response (UPR)

A cellular stress response to misfolded proteins in the ER lumen. The UPR includes a complex signaling cascade to fold or remove the unfolded proteins, or to induce apoptosis

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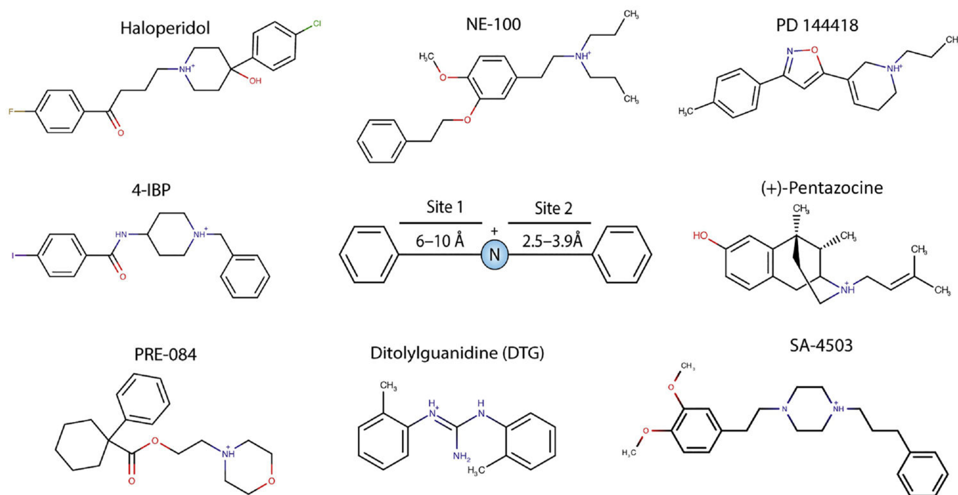

Figure 1: Representative σ receptor ligands and the central pharmacophore.

A depiction of some high-affinity σ receptor ligands, as well as the central σ_1 receptor pharmacophore. Adapted from Glennon et al., 2005 [19].

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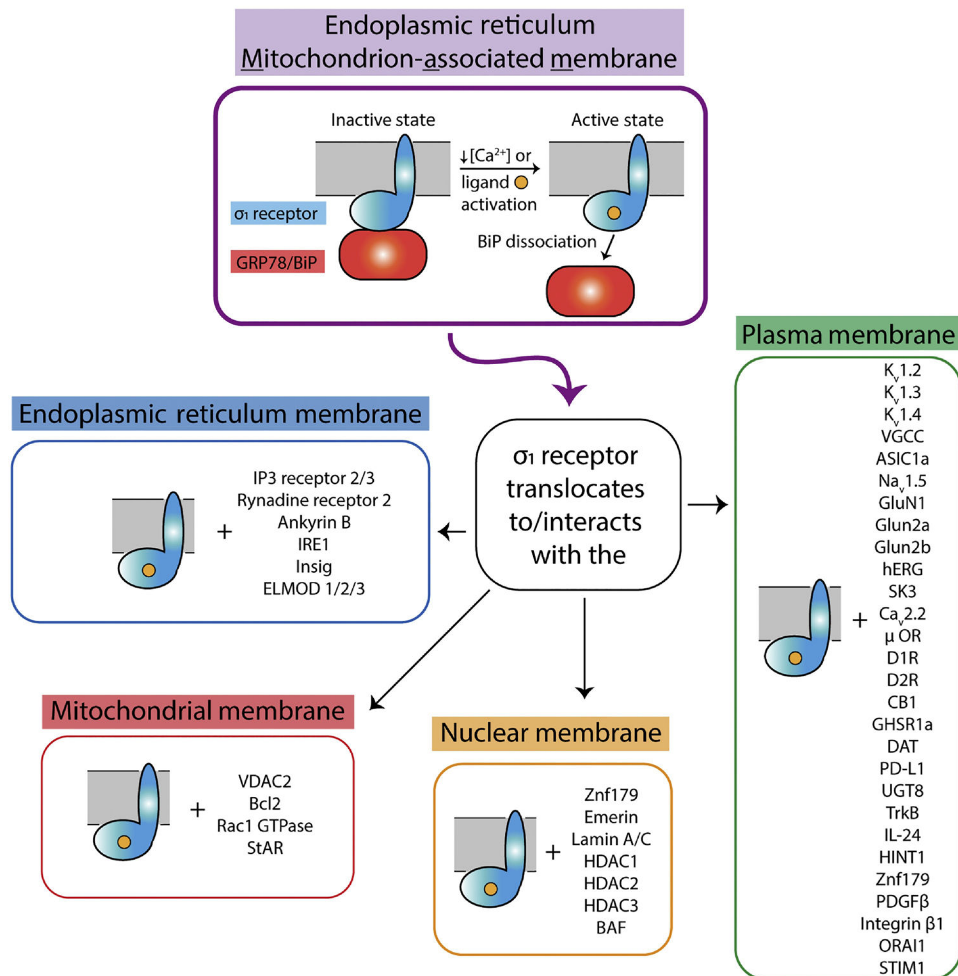

Figure 2: A summary of the chaperone model for σ_1 receptor function.

The σ_1 receptor has been proposed to act as a ligand-regulated chaperone to modulate multiple signaling pathways. Based on the text from Weng et al. [5]. Interaction partners are taken from the references in Table 1, and the localization of each partner was based on both the references in Table 1 and the Uniprot localization annotations for those proteins.

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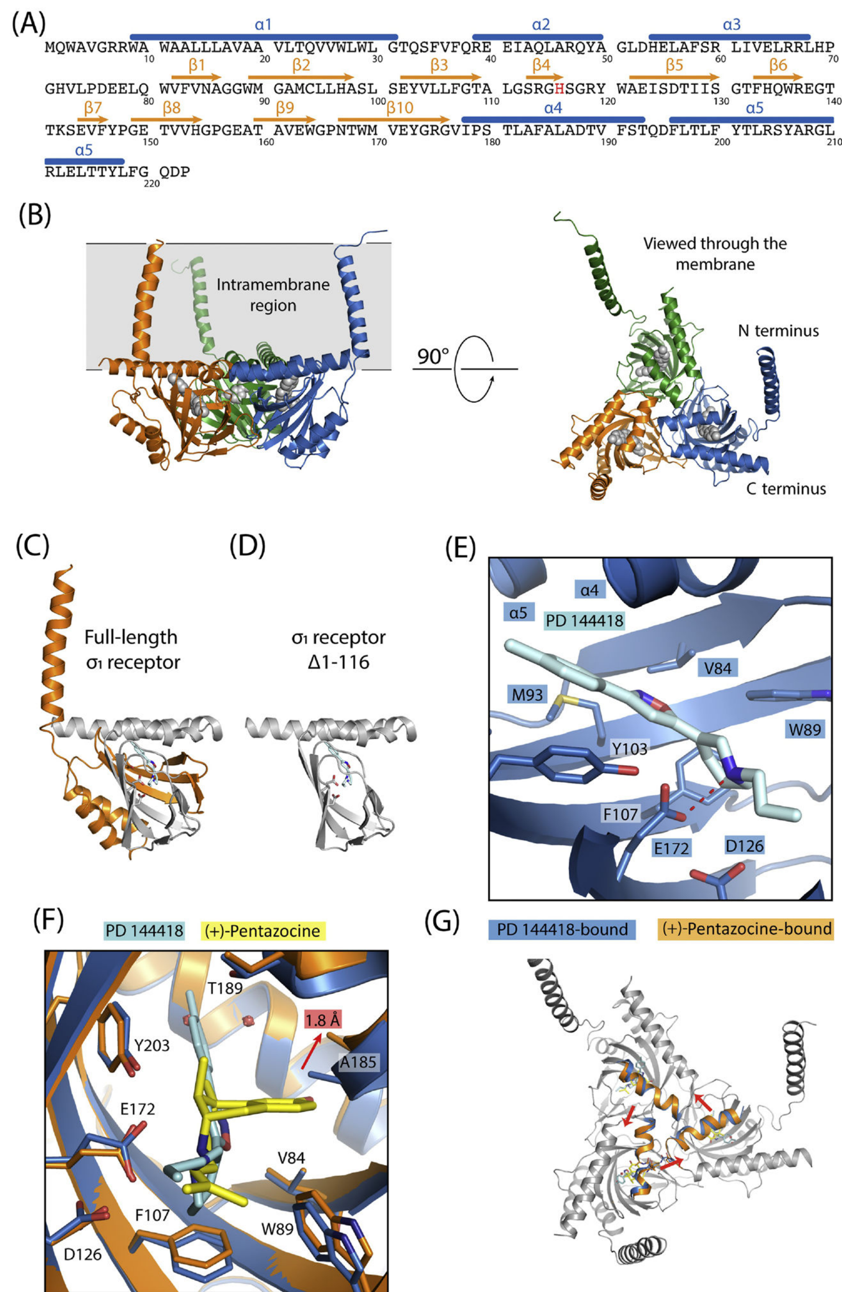

Figure 3: The structure of the σ_1 receptor.

(A) the σ_1 receptor's amino acid sequence annotated by secondary structure, with α helices in blue and β sheets in orange. Histidine 116 is in red. (B) the structure of the human σ_1 receptor (PDB ID: 5HK1). Each σ_1 monomer is colored separately, and the membrane is represented by gray shading. The ligand PD 144418 is depicted in grey spheres. (C), (D), a σ_1 receptor monomer, with amino acids 1–116 colored in orange (C) or hidden completely (D), to show parts of the protein that would remain if these residues were deleted. (E) a view of the ligand binding pocket (PDB ID: 5HK1). The red dashed line shows electrostatic interaction between the Glu172 and the basic nitrogen in the ligand. (F) Overlays of the structures of the σ_1 receptor bound to the antagonist PD 144418 (PDB ID: 5HK1, blue) and

the agonist (+)-pentazocine (PDB ID: 6DK1, orange). The red arrow shows the shift in helix α4 between the two structures. Waters unique to the (+)-pentazocine bound structure are depicted as red spheres. (G) The same overlay as in (F), but only helix α4 is colored and the rest of the receptor is shown in gray. Red arrows indicate the direction of the α4 shift induced by (+)-pentazocine.

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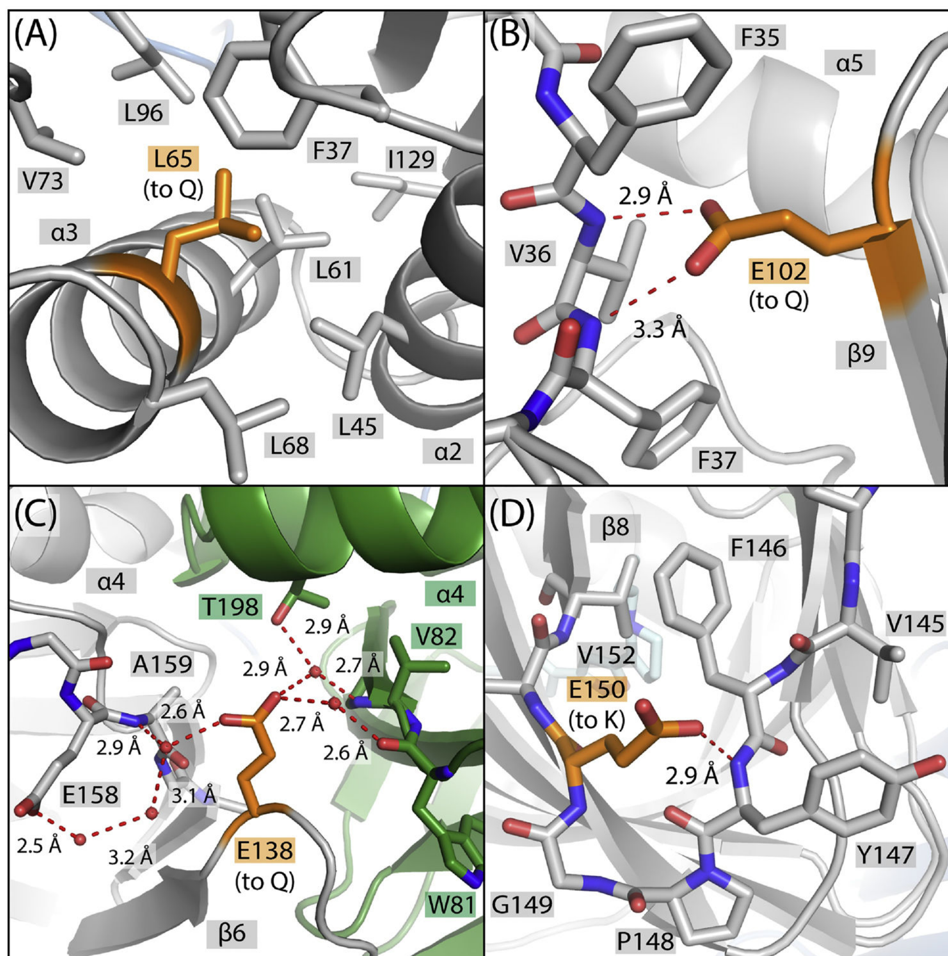

Figure 4: Structural locations of σ_1 receptor disease mutations.

The crystal structure of the σ_1 receptor with amino acids L65, E102, E138, and E150 of chain A shown in orange, while the rest of chain A is shown in grey. Chains B and C are shown in blue and green, respectively. Dashed red lines represent hydrogen bonds. PD 144418 is shown in cyan. Waters are depicted as red spheres. (A), L65 is located on helix α4 and is surrounded by hydrophobic amino acids. Mutation to Q would likely be energetically unfavorable. (B), E102 makes two hydrogen bonds with backbone amide nitrogen atoms. Mutation to Q would replace one of these attractive bonds with a repulsive interaction, presumably destabilizing the protein. (C), E138 coordinates a complex network of water molecules and amino acids at the oligomeric interface. Mutation to Q would disrupt this network. (D), E150 makes a hydrogen bond with a backbone amide nitrogen to stabilize the β hairpin at the base of the ligand binding pocket's "lid". Mutation to K would prevent this interaction.

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Table 1:

List of reported experiments positing σ_1 receptor protein-protein interactions.

A list of published experiments that have been used to suggest direct protein-protein interactions between the σ_1 receptor and other proteins. For constructs, the name of the proteins/tags are listed from N- to C-terminus, such that tags on the N-terminus precede the name of the protein, while tags on the C-terminus proceed the name of the protein. Only interactions reported using low-throughput methods are shown. For the purposes of this table, a "pull down" refers to experiments where at least one of the components was purified. Co-IP: co-immunoprecipitation, BRET: bioluminescence resonance energy transfer, HTRF: homogenous time-resolved fluorescence, SRET: sequential resonance energy transfer, NMR: nuclear magnetic resonance, BiFC: bimolecular fluorescence complementation.

Protein partner	Human gene	Method	σ_1 receptor construct	Protein partner construct	Cell/tissue type	Expression method	Refs
Ion channels							
Inositol triphosphate receptor (IP3R)	ITPR3	Co-IP	Native σ_1 receptor	Native IP3R	NG-108 cells	Native expression	[33]
		Co-IP	Native σ_1 receptor	Native IP3R	CHO cells	Native expression	[21]
		Co-IP	σ_1 receptor-EGFP	Native IP3R	NG-108 cells	Transient overexpression (σ_1 receptor)	
						Native expression (IP3R)	
		Co-IP	σ_1 receptor-EGFP	Native IP3R	CHO cells	Transient overexpression (σ_1 receptor)	
						Native expression (IP3R)	
		Co-IP	Native σ_1 receptor	Native IP3R	Isolated bovine brain mitochondria	Native expression	[100]
	ITPR1	Co-IP	Native σ_1 receptor	Native IP3R	NG-108 cells	Native expression	[101]
		Proximity ligation	Native σ_1 receptor	Native IP3R	NG-108 cells	Native expression	
	ITPR2	Co-IP	Native σ_1 receptor	Native IP3R	Rat heart tissue	Native expression	[102]
Rynadine receptor 2 (RYR2)	RYR2	Co-IP	Native σ_1 receptor	Native RYR2	Rat heart tissue	Native expression	[102]
$K_v1.2$ K^+ channel	KCNA2	Co-IP	Native σ_1 receptor	Native $K_v1.2$	Mouse nucleus accumbens lysate	Native expression	[38]
		Co-IP with cross-linking	σ_1 receptor-V5-His	Wildtype $K_v1.2$	NG108–15 cells	Transient overexpression	
$K_v1.3$ K^+ channel	KCNA3	Co-IP	σ_1 receptor-FLAG	$K_v1.3$-HA	HEK 293 cells	Transient overexpression	[103]
$K_v1.4$ K^+ channel	KCNA4	Co-IP	Native σ_1 receptor	Native $K_v1.4$	Rat posterior pituitary lysate	Native expression	[34]

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Protein partner	Human gene	Method	σ_1 receptor construct	Protein partner construct	Cell/tissue type	Expression method	Refs
L-type voltage-gated calcium channel (VGCC)	CACNA1C	Co-IP	Wildtype σ_1 receptor	Native L-type VGCC	RGC-5 cells	Stable overexpression (σ_1 receptor in some experiments)	[104]
						Native expression (VGCC, and σ_1 receptor in one experiment)	
Acid-sensing ion channel 1a (ASIC1a)	ASIC1	Ni affinity chromatography	σ_1 receptor-FLAG-His	ASIC1a-His	HEK 293 cells	Stable overexpression (ASIC1a) Transient	[57]
						overexpression (σ_1 receptor)	
$Na_v1.5$ Na^+ channel	SCN5A	Anti-FLAG chromatography	σ_1 receptor-FLAG	$Na_v1.5$-HA	tSA 201 cells	Transient overexpression	[37]
		Proximity ligation					
		Co-IP	Native σ_1 receptor	Native $Na_v1.5$	MDA-MB-468 cells	Native expression	[35]
		Co-IP	Native σ_1 receptor	Native $Na_v1.5$	MDA-MB-231 cells	Native expression	
N-methyl-*D*-aspartate receptor (NMDAR) GluN1 subunit	GRIN1	Anti-FLAG chromatography	σ_1 receptor-FLAG	Wildtype GluN1	tsA 201 cells	Transient overexpression	[36]
		Anti-FLAG chromatography	σ_1 receptor-FLAG	Wildtype GluN1	NG108–15 cells	Transient overexpression	
		Proximity ligation	σ_1 receptor-FLAG	GluN1-HA	tsA 201 cells	Transient overexpression	
		Pull down	σ_1 receptor-TEV	GluN1 c-terminal fragment C0-C1-C2	Purified Protein	Bacterial expression and purification	[105]
		Pull down	σ_1 receptor-TEV	GluN1 c-terminal fragment C0-C1-C2	Purified Protein	Bacterial expression and purification	[106]
		Pull down	σ_1 receptor-TEV	GluN1 c-terminal fragment C0-C1-C2	Purified Protein	Bacterial expression and purification	[107]
		BiFC	S1R-split Venus	GluN1-split Venus	CHO cells	Transient overexpression	[108]
NMDAR Glun2a subunit	GRIN2a	Co-IP	Native σ_1 receptor	Native GluN2a	Rat hippocampus P2 pellet	Native expression	[59]
NMDAR Glun2b subunit	GRIN2b	Co-IP	Native σ_1 receptor	Native GluN2a	Rat hippocampus P2 pellet	Native expression	[59]
Human ether-a-go-go channel (hERG)	KCNH2	Co-IP	σ_1 receptor-Myc	Wildtype hERG	HEK 293 cells	Transient overexpression (σ_1 receptor)	[60]

Protein partner	Human gene	Method	σ_1 receptor construct	Protein partner construct	Cell/tissue type	Expression method	Refs
						Stable overexpression (hERG)	
		Anti-Myc chromatography	myc-σ_1 receptor	hERG with HA tag between residues 443–444	tsA 201 cells	Transient overexpression	[58]
		Proximity ligation	myc-σ_1 receptor	hERG with HA tag between residues 443–444	tsA 201 cells	Transient overexpression	[58]
		HTRF	myc-σ_1 receptor-HALO	hERG with HA tag between residues 443–444	HEK 293 cells	Transient overexpression	[58]
SK3 channel	KCNN3	Co-IP	σ_1 receptor-Myc	Wildtype SK3	SKmel28 cells	Transient overexpression (σ_1 receptor)	[109]
SK3 channel	KCNN3	Co-IP	σ_1 receptor-Myc	Wildtype SK3	SKmel28 cells	Stable overexpression (SK3)	[109]
SK3 channel	KCNN3	HTRF	HALO-σ_1 receptor-Myc	SK3-HA	HEK 293 cells	Transient overexpression	[109]
Voltage-dependent N-type calcium channel ($Ca_v2.2$)	CACNA1B	FRET	σ_1 receptor-dsred	EGFP-Cav2.2	HEK 293T cells	Transient overexpression	[51]
Voltage-dependent N-type calcium channel ($Ca_v2.2$)	CACNA1B	Co-IP	σ_1 receptor-dsred	EGFP-$Ca_v2.2$	HEK 293T cells	Transient overexpression	[51]
Voltage-dependent anion channel 2 (VDAC2)	VDAC2	Co-IP	Native σ_1 receptor	Native VDAC2	MA-10 cells	Native expression	[110]
Calcium release-activated calcium channel protein 1	ORAI1	Co-IP	σ_1 receptor-FLAG	ORAI1-Myc	tsA 201 cells	Transient overexpression	[39]
G-protein coupled Receptors (GPCRs)							
μ opioid receptor (μ OR)	OPRM1	Co-IP	σ_1 receptor-HA	FLAG-μ OR	HEK 293T cells	Transient overexpression	[40]
μ opioid receptor (μ OR)	OPRM1	Pull down	σ_1 receptor-TEV	μ OR (res. 286–398)	Purified protein	Bacterial expression and purification	[105]
D1 dopamine receptor (D1R)	DRD1	BRET	σ_1 receptor-YFP	D1R-Rluc	HEK 293T	Transient overexpression	[41]
D1 dopamine receptor (D1R)	DRD1	BRET	σ_1 receptor-Rluc	D1R-YFP	HEK 293T	Transient overexpression	[41]
D1 dopamine receptor (D1R)	DRD1	BRET	σ_1 receptor-Rluc	YFP-D1R	HEK 293T	Transient overexpression	[41]
D1 dopamine receptor (D1R)	DRD1	SRET	σ_1 receptor-YFP	D1R-GFP	HEK293T	Transient overexpression	[42]
D1 dopamine receptor (D1R)	DRD1	Co-IP	Native σ_1 receptor	Native D1R	Mouse striatal slices	Native expression	[42]

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Protein partner	Human gene	Method	σ_1 receptor construct	Protein partner construct	Cell/tissue type	Expression method	Refs
		Proximity ligation	Native σ_1 receptor	Native D1R	Mouse striatal slices	Native expression	
D2 dopamine receptor (D2R)	DRD2	BRET	σ_1 receptor-YFP	D2R-Rluc	HEK 293T	Transient overexpression	[43]
		Proximity ligation	Native σ_1 receptor	Native D2R	Rat brain sections	Native expression	[44]
Cannabinoid receptor 1 (CB1)	CNR1	Co-IP	Native σ_1 receptor	Native CB1	Mouse brain synaptosomes	Native expression	[108]
		BiFC	σ_1 receptor-split Venus	CB1 split-Venus	CHO cells	Transient overexpression	
Ghrelin receptor 1a (GHSR1a)	GHSR	BRET	σ_1 receptor-YFP	GHSR1a-Rluc	HEK 293T	Transient overexpression	[45]
		Proximity ligation	Native σ_1 receptor	Native GHSR1a	Primary rat striatal neurons	Native expression	
Other proteins							
Ankyrin B	ANK2	Co-IP	Native σ_1 receptor	Native ankyrin B	NG-108 cells	Native expression	[33]
		Co-IP	Wildtype σ_1 receptor	Native ankyrin B	MCF-7 cells	Stable overexpression (σ_1 receptor) Native expression (ankyrin B)	[77]
		Co-IP	σ_1 receptor (res. 102–223)	Native ankyrin B	MCF-7 cells	Stable overexpression (σ_1 receptor) Native expression (ankyrin B)	
Binding immunoglobulin protein (BiP)	GRP78	Co-IP with crosslinking	σ_1 receptor-YFP	Native BiP	CHO cells	Stable overexpression (σ_1 receptor) Native expression (BiP)	[21]
		Pull down	σ_1 receptor (res.116–223)	Unknown source of recombinant BiP[1]	Purified protein	Bacterial expression and purification	
		NMR	σ_1 receptor (res.112–223)	Human BiP (res.24–654)	Purified protein	Bacterial expression and purification	[76]
		Co-IP	Native σ_1 receptor	Native BiP	Isolated bovine brain mitochondria	Native expression	[100]
		Co-IP with crosslinking	σ_1 receptor-YFP	Native BiP	Neuro2A cells	Transient overexpression (σ_1 receptor) Native expression (BiP)	[111]
Dopamine transporter (DAT)	DAT	Co-IP	GST-σ_1 receptor	myc-DAT	HEK 293 cells	Transient overexpression	[61]

Protein partner	Human gene	Method	σ_1 receptor construct	Protein partner construct	Cell/tissue type	Expression method	Refs
		Co-IP	Wildtype σ_1 receptor	Wildtype DAT	HEK 293 cells	Transient overexpression	
		BRET	σ_1 receptor-Rluc	venus-DAT	HEK 293 cells	Transient overexpression	
PD-L1	CD274	Co-IP	σ_1 receptor-HA	PD-L1-FLAG	MDA-MB-231 cells	Transient overexpression	[62]
Cerebroside synthase (UGT8)	UGT8	Co-IP with crosslinking	σ_1 receptor-V5	UGT8-Myc	CHO cells	Transient overexpression	[64]
IRE1	ERN1	Co-IP	σ_1 receptor-V5	Native IRE1	CHO cells	Transient overexpression	[63]
		Pull down	σ_1 receptor (res.116–223)	IRE1 (res.19–443)-V5-His	Purified protein	Bacterial expression and purification	
TrkB	NTRK2	Co-IP	σ_1 receptor-Myc	HA-TrkB	HEK 293T cells	Transient overexpression	[112]
		Co-IP	Native σ_1 receptor	Native TrkB	Mouse cerebellar granule neurons	Native expression	
IL-24	IL24	Co-IP	Native σ_1 receptor	Wildtype IL-24	DU145 cells	Native expression (σ_1 receptor)	[113]
						Viral overexpression (IL-24)	
Bcl2	BAD	Co-IP	Native σ_1 receptor	Native Bcl2	Isolated bovine brain mitochondria	Native expression	[100]
Rac1 GTPase	RAC1	Co-IP	Native σ_1 receptor	Native Rac1 GTPase	Isolated bovine brain mitochondria	Native expression	[100]
HINT1	HINT1	Pull down	σ_1 receptor-GST	Wildtype HINT1	Purified protein	Bacterial expression and purification	[105]
Znf179	RNF112	Co-IP	σ_1 receptor-His	Native Znf179	Neuro2A cells	Transient overexpression (σ_1 receptor)	[114]
						Native expression (Znf179)	
Insig	INSIG1	Co-IP	σ_1 receptor-FLAG	Insig-Myc	CHO cells	Transient overexpression	[64]
ELMOD1	ELMOD1	Co-IP	FLAG-σ_1 receptor	GST-ELMOD1	HEK 293T cells	Transient overexpression	[115]
ELMOD2	ELMOD2	Co-IP	FLAG-σ_1 receptor	GST-ELMOD1	HEK 293T cells	Transient overexpression	[115]
ELMOD3	ELMOD3	Co-IP	FLAG-σ_1 receptor	GST-ELMOD1	HEK 293T cells	Transient overexpression	[115]
Steroidogenic acute regulatory protein (StAR)	STAR	Co-IP	Native σ_1 receptor	Native StAR	MA-10 cells	Native expression	[110]

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Protein partner	Human gene	Method	σ_1 receptor construct	Protein partner construct	Cell/tissue type	Expression method	Refs
Platelet derived growth factor β (PDGFβ)	PDGFRB	Pull down	Wildtype σ_1 receptor	GST-PDGFβ	HEK 293T cells lysate (σ_1 receptor)	Transient overexpression (σ_1 receptor)	[116]
					Purified protein (PDGFβ)	Insect cell expression and purification (PDGFβ)	
		FRET	σ_1 receptor-RFP	PDGFβ-GFP	CHO cells	Transient overexpression	
Integrin β1	IGTB1	Co-IP	Native σ_1 receptor	Native Integrin β1	MDA-MB-231 cells	Native expression	[117]
Emerin	EMD	Co-IP with crosslinking	σ_1 receptor-YFP	Native Emerin	Neuro2A cells	Transient overexpression (σ_1 receptor)	[111]
						Native expression (Emerin)	
		Co-IP with crosslinking	σ_1 receptor-V5-His	Native Emerin	Neuro2A cells	Transient overexpression (σ_1 receptor)	
						Native expression (Emerin)	
		Co-IP	Native σ_1 receptor	Native Emerin	Rat nucleus accumbens tissue	Native expression	
		Co-IP	Native σ_1 receptor	Native Emerin	Mouse prefrontal cortex tissue	Native expression	
Lamin A/C	LMNA	Co-IP with crosslinking	σ_1 receptor-YFP	Native Lamin A/C	Neuro2A cells	Transient overexpression (σ_1 receptor)	[111]
						Native expression (Lamin A/C)	
		Co-IP with crosslinking	σ_1 receptor-V5-His	Native Lamin A/C	Neuro2A cells	Transient overexpression (σ_1 receptor)	
						Native expression (Lamin A/C)	
Histone deacetylase 1 (HDAC1)	HDAC1	Co-IP	Native σ_1 receptor	Native HDAC1	Neuro2A cells	Native expression	[111]
		Co-IP	Native σ_1 receptor	Native HDAC1	Mouse prefrontal cortex tissue	Native expression	
		Co-IP	Native σ_1 receptor	Native HDAC1	NG-108 cells	Native expression	
Histone deacetylase 2 (HDAC2)	HDAC2	Co-IP	Native σ_1 receptor	Native HDAC2	Neuro2A cells	Native expression	[111]
		Co-IP	Native σ_1 receptor	Native HDAC2	Mouse prefrontal cortex tissue	Native expression	

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Protein partner	Human gene	Method	σ_1 receptor construct	Protein partner construct	Cell/tissue type	Expression method	Refs
		Co-IP	Native σ_1 receptor	Native HDAC2	NG-108 cells	Native expression	
Histone deacetylase 3 (HDAC3)	HDAC3	Co-IP	Native σ_1 receptor	Native HDAC3	Neuro2A cells	Native expression	[111]
		Co-IP	σ_1 receptor-V5-His	Native HDAC3	Neuro2A cells	Transient overexpression (σ_1 receptor)	
						Native expression (HDAC3)	
Barrier-to autointegration-factor (BAF)	BANF1	Co-IP	Native σ_1 receptor	Native BAF	Neuro2A cells	Native expression	[111]
Stromal interaction molecule 1	STIM1	Co-IP	σ1 receptor-FLAG	HA-STIM1	tSA 201 cells	Transient overexpression	[39]

[1]The source of the recombinant BiP used in this paper is not stated.

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Table 2:

List of pathogenic human σ_1 receptor mutations and their cellular effects.

A list of published mutations in the human SIGMAR1 gene that exhibit disease phenotypes. Only mutations reported in cohort studies are shown.

Variant	Location on gene	Amino acid change	Phenotype	Cellular effect
c.151+1G>T	Exon 1 splice site	31–50	dHMN [81]	Mislocalization [118]
c.194T>A	Exon 2	L65Q	dHMN/SS [83]	Unknown
c.283dupC	Exon 2	L95P + frameshift	ALS [79, 119]	Aberrant ER morphology [119]
c.304G>C	Exon 2	E102Q	ALS [78]	Misfolding, ER stress [120], mislocalization [118]
c.412G>C	Exon 3	E138Q	dHMN [82]	Mislocalization, aberrant ER function [82]
c.448G>A	Exon 4	E150K	dHMN [82]	Mislocalization, aberrant ER function [82]
c.561_576del	Exon 4	Stop codon after H69	dHMN [84]	Unknown
Exon 4 deletion	Exon	Deletion of residues 69–223	dHMN [84]	Unknown
c.672*31A>G	3’ UTR	None	ALS [80]	Unknown
c.672*51G>T	3’ UTR	None	FTLD-MND [85]	Increased mRNA expression [85]