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Trends Pharmacol Sci. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:
Trends Pharmacol Sci. 2016 April ; 37(4): 262–278. doi:10.1016/j.tips.2016.01.003.

Sigma-1 Receptor as a Pluripotent Modulator in the Living System

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Abstract

The sigma-1 receptor (Sig-1R) is an endoplasmic reticulum (ER) protein resides specifically at the interface between ER and mitochondria, called the MAM, where the Sig-1R is recently reported to be involved in certain CNS diseases. In addition to being able to translocate to the plasma membrane to interact with ion channels and other receptors, the Sig-1R is found to exist at the nuclear envelope where it recruits chromatin-remodeling factors to affect the transcription of genes. As well, thorough experimental and bioinformatic means, Sig-1Rs are reported to interact with other membranous or soluble proteins at other loci, including the cytosol. We propose that the Sig-1R is a pluripotent modulator with resultant multiple functional manifestations in the living system.

Keywords

Sigma-1 receptor; Pluripotent modulator; Diseases

The Sigma-1 Receptor: Brief History and Current Status

Martin *et al*. [1] hypothesized the existence of multiple opioid receptors to mediate different pharmacological effects of morphine and it various structural analogs. These receptors and their prototypic ligands and pharmacological effects are respectively: mu opioid receptor (MOR) for morphine-induced analgesia, kappa opioid receptor for ketocyclazocine-induced dysphoria, and sigma “opioid” receptor for SKF-10047 (N-normetazocine)-induced psychotomesis. Influenced by the multiple opioid receptor hypothesis, Su [2] demonstrated the existence of a “sigma receptor” that however differs from Martin’s sigma “opioid” receptor in that the sigma receptor discovered by Su has very low affinity for naltrexone which is a universal high-affinity blocker for all subtypes of opioid receptors as hypothesized by Martin et al..

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The sigma receptor discovered by Su therefore is a receptor on its own and is not a subtype of opioid receptors. The sigma receptor identified by Su was unfortunately mistermed as the sigma "opioid" receptor in its original publication [2] but was later correctly called the sigma receptor [3]. The sigma receptor identified by Su was later recognized as the sigma-1 receptor (Sig-1R) when two subtypes of the sigma receptor were identified as Sig-1R and Sig-2R [4]. The Sig-1R has been cloned and was found to be an ER protein (Box 1) [5]. The Sig-2R has not been cloned so far. Although the progesterone receptor membrane component 1 was suggested to be the Sig-2R [6], the final identification remains to be fully clarified and awaits the confirmation by successful cloning and sequencing of the Sig-2R in the future.

The Sig-1R is mainly an ER protein where it resides specifically at the ER-mitochondrion interface, referred to as the MAM (mitochondrion-associated ER membrane) [7]. A the MAM, the Sig-1R acts as a molecular chaperone and sustains the proper conformation of the inositol triphosphate (IP3) receptor type 3 to ensure proper Ca2+ signaling from the ER into mitochondria to facilitate the production of ATP [7–9]. At the MAM, the Sig-1R also chaperones an ER stress sensor, inositol-requiring enzyme 1 (IRE1), to ensure the proper transmission of ER stress into the nucleus to call for the enhanced production of anti-stress and antioxidant proteins [10]. Sig-1Rs also attenuate the formation of reactive oxygen species (ROS) by enhancing the signaling of Nrf2 [11].

The Sig-1R can, upon the stimulation of agonists or stress, translocate to the plasma membrane to interact with ion channels, receptors, and kinases [12, 13]. The Sig-1R is also found to translocate to the envelope of the nucleus [14, 15], where the Sig-1R interacts with a nuclear envelope-resident protein emerin and recruits therein a series of chromatin-remodeling factors to regulate the gene transcription [15]. Recently, many studies via experimental or bioinformatics means have identified or proposed the interaction of the Sig-1R with many other functional proteins in the plasma membrane, ER, mitochondria, and even the cytosol.

The above results, when taken together, suggest that the Sig-1R acts as a pluripotent modulator in the living system that may thus affect many human diseases. In this opinion, we report those proteins that have been experimentally shown to interact with the Sig-1R (Figure 1), and other proteins that were reported to link to the Sig-1R via bioinformatics information (Figure 2). We also show in particular the CNS diseases that have been reported to relate to the Sig-1R (Table 1). Collectively, current research findings suggest that the Sig-1R, as a pluripotent modulator via its interactions with diverse classes of other proteins, may play important physiological roles in the living system and that the dysfunction of the Sig-1R may contribute to certain human diseases.

Sig-1R–interacting proteins per experimental demonstrations including co-immunoprecipitation and proximity assessment experimentations

At the Plasma Membrane

Regardless of its predominant ER membrane expression pattern, many reports demonstrate that the Sig-1R also regulates plasma membrane proteins (Figure 1). The following section

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briefly reviews all plasma membrane proteins that have been reported so far to interact directly with the Sig-1R.

Acid-sensing ion channels (ASICs)—ASICs are proton-gated cation channels expressed in the peripheral and central nervous neurons and can be activated by acidic pH conditions that occur for example during ischemia.

Sig-1Rs can modulate ASICs via the activation of Sig-1Rs by ligands and inhibits thus ASIC1a–induced calcium influx in rat cortical neurons [16]. However, direct interaction between Sig-1Rs and ASIC1a was later demonstrated by atomic force microscopy imaging. The analysis of the Sig-1R binding to ASIC1a was carried out in cells coexpressing ASIC1a and FLAG/His6-tagged Sig-1R. The results of the stoichiometry suggested that the Sig-1R associates with the trimeric ASIC1a subunit with a 3-fold symmetry [17]. However, opinions differ in those two types of studies in whether the interaction of the Sig-1R and the ASIC1a takes place in lipid rafts.

Dopamine receptors—Dopamine receptors (DR) play crucial roles in many neurological processes, including motivation, cognition, memory, and motor function. There are at least five subtypes of dopamine receptors: D1, D2, D3, D4, and D5. Moreover, those receptors are grouped as D1-like receptor (D1 and D5) and D2-like receptor (D2, D3, and D4), which respectively stimulate or inhibit adenylyl cyclase.

Navarro and colleagues [18] demonstrated the heterodimerization of Sig-1R and dopamine D1 receptor (D1R) in living cells using bioluminescent resonance energy transfer saturation experiments. Colocalization of Sig-1R and D1R was also identified by immunostaining studies. The Sig-1R-D1R interaction was later extended to animal tissue, where Sig-1R-D1R-Histamine H3 receptor complexes were detected in the rat striatum by energy transfer experiments and proximity ligation assays [19]. A similar approach was applied to establish the functional interaction of Sig-1R and D2R. The data suggest that cocaine binds to Sig-1R-D2R heteromers and inhibits the downstream extracellular-signal-regulated kinase-MAPK signaling pathway [20]. These findings suggest that the Sig-1R binds D1R and D2R and thus differentially associates and modulates the D1R and D2R downstream signaling when neurons are stimulated by cocaine.

Muscarinic acetylcholine receptor (mAchR)—mAchRs are G protein-coupled receptors for acetylcholine that plays important roles in the control of motor neurons in the brain.

In a ventral horn motorneuron model, Mavlyutov *et al*. [21] examined the distributions of Sig-1Rs at the synaptic contact site. Immunoelectron microscopy revealed that Sig-1Rs are located in the postsynaptic densities and are juxtapositional to the metabotropic acetylcholine receptor (mAchR) M2 in very close proximity. The ultrastructure visualization of Sig-1Rs indicated that Sig-1Rs are excluded from the PM; rather, they are primarily located in the subsurface ER cisternae. Since the interaction between Sig-1R and mAchRM2 may promote the survival or proper functioning of motor neurons, the close proximity of the

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Sig-1R to mAchRM2 suggests a role of the Sig-1R in amyotrophic lateral sclerosis whose hallmark is the motor neuron degeneration.

Mu-opioid receptor (MOR)—The MOR is a subtype of opioid receptors that mediates morphine-induced analgesia. Although the Sig-1R is not a subtype of opioid receptors, as stated in the introduction, numerous studies have been focused on the endogenous Sig-1R as the negative modulator of opioid analgesia [22–26]. As such, Sig-1R antagonists would potentiate morphine-induced analgesia. The functional and physical association of Sig-1R with MOR was recently assessed by the guanosine 5′-O-(3-[35S]thio)triphosphate ([35S]GTPγS) binding and by coimmunoprecipitation experiments using epitope-tagged receptors [27]. Interestingly, this study also showed that, in mouse brain membrane preparations, Sig-1R-selective antagonists could potentiate both opioid receptor and muscarinic acetylcholine receptor-mediated stimulation of [(35)S]GTP gamma S binding. These results suggest a broader role for Sig-1Rs in modulating G-protein-coupled receptor signaling [27].

The Sig-1R also has been demonstrated to modulate opioid analgesia through the Sig-1R′s interaction with the NMDA receptor NR1 subunit (GluN1) [28] (see next section). The potential role of Sig-1R in the cross-regulation between MOR and NMDARs was demonstrated by using peptide interference assay and immunohistochemistry in the mouse mesencephalic periaqueductal grey matter. Those results suggest that the Sig-1R-MOR-GluN1 trimeric complex may play a role in nociception. However, further investigation is needed to totally clarify the relation between the trimeric complex and MOR-induced analgesia.

N-methyl-D-aspartate receptor (NMDAR) and Cannabinoid Receptor 1 (CB1R)—The NMDA receptor is an ion channel type of receptor for glutamate and consists of a heterotetramer between two GluN1 and two GluN2 subunits. The NMDAR controls certain neuronal functions including synaptic plasticity and memory. The CB1R is a G protein-coupled receptor for endocannabinoids such as anandamide and 2-arachidonoylglycerol and is expressed at presynaptic neurons where the CB1R modulates the release of neurotransmitter glutamate.

The Sig-1R has been extensively studied in cognitive function, particularly in psychiatric disorders. Sig-1R agonists have shown to enhance NMDAR functionality [29, 30]. Combining the atomic force microscopy imaging study and the *in situ* proximity ligation assay, Balasuriya et al. [31] demonstrated a direct interaction between the Sig-1R and NMDAR. The Sig-1R bound directly to the NMDAR subunits, GluN1/GluN2A heterotetramers, specifically via the interaction with the GluN1 subunit. Interestingly, the Sig-1R agonist administration caused an upregulation of GluN2A and GluN2B expression in the synaptosomal fraction [32]. The Sig-1R antagonist abolished the agonist-induced increase of synaptosomal expression of GluN2A and GluN2B and their associated trafficking to the plasma membrane. Coimmunoprecipitation studies also revealed an increased interaction between Sig-1Rs and GluN2 subunits by Sig-1R agonist [32]. A recent study suggested that the Sig-1R functions as a safety switch to control CB1-NMDAR interaction to prevent CB1R–provoked NMDAR hypofunction [33]. The interactions of

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Sig-1Rs with CB1R, GluN1 and the histidine triad nucleotide-binding protein 1 (HINT1) were visualized by bimolecular fluorescence complementation assay. The data suggested that the assembly of the CB1-HINT1-GluN1 protein complex is critically regulated by the Sig-1R. These findings indicate that the Sig-1R regulates synaptic plasticity perhaps via dynamic protein associations. The main function of the Sig-1R in this regard is suggested to allow for the restoration of the hypo-functional NMDAR that was caused by the interacting CB1R. The authors proposed that this action of the Sig-1R regulates the homeostasis between opposite effects of CB1R and NMDAR in the context of analgesia and certain psychiatric disorders like schizophrenia. The hypo-functional NMDAR has been implicated in schizophrenia.

Tropomyosin receptor kinase B (TrkB)—The TrkB is cell surface tyrosine kinase receptor for brain derived neurotrophic factor (BDNF) and neurotrophin 4. TrkB plays important roles in the brain including synaptic transmission, neurogenesis, learning, and cognition.

Sig-1R agonists exert anti-depressant-like effects and neuroprotective effects via the upregulation of BDNF [34] or the enhanced post-translational processing of BDNF [35]. In addition, Kimura *et al*. [36] reported that the Sig-1R interacts with the BDNF receptor TrkB in cerebellar granule neurons and promotes the neurite elongation. The report also demonstrated that the coimmunoprecipitation of Sig-1R and TrkB was apparently strengthened by the Sig-1R agonist PRE-084.

Platelet-derived growth factor receptor (PDGFR)—The PDGFR is cell surface tyrosine kinase receptor for PDGF and plays a role in the regulation of cell proliferation, cellular differentiation, cell growth, and development, and relates to many diseases including cancer.

It has been known that the Human immunodeficiency virus (HIV)-associated increase in monocyte adhesion and trafficking is exacerbated by cocaine abuse. One of the underlying mechanisms involves cocaine-mediated upregulation of cell adhesion molecules that result in subsequent disruption of the blood-brain barrier. PDGFR is known to cause the transcriptional increase of an adhesion molecule called ALCAM by activating the transcription factor nuclear factor-kB. However, the exact relationship between the HIV-related action of cocaine and PDGFR remained unknown until the study below was published.

In human brain microvascular endothelial cells, the Sig-1R can interact with the PDGFR and the interaction was intensified by cocaine as a result of cocaine causing the translocation of the Sig-1R from the MAM to the plasma membrane [37]. This interaction of the Sig-1R with PDGFR is important for cocaine to enhance the transmigration or infiltration of leukocytes across the blood-brain barrier by increasing the expression of ALCAM. Further, as nuclear factor -kB also mediates inflammation, the Sig-1R-PDGFR interaction plays an important role in the HIV-induced inflammation which is also known to be exacerbated by cocaine.

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Integrin-β_1—Integrins are transmembrane receptors for cell adhesion molecules including fibronectin and collagen, and are important for the metastasis of cancer cells. Integrin is a heterodimers consisting of α and β subunits.

The Sig-1R has been reported to interact with integrin-β_1 which facilitates cell adhesion [38]. Interestingly, the interaction between Sig-1R and integrin-β_1 was blocked by the Sig-1R ligand SKF-10047, which is a Sig-1R agonist. Further, the silencing of Sig-1Rs by siSig-1R attenuated cell adhesion. Those two seemingly contradictory results, agonist producing the same effect as that from siRNA treatment, need to be clarified in the future. Nevertheless, the interaction between Sig-1R and integrin-β_1 suggests a role of the Sig-1R in cell adhesion and perhaps the progression of cancer cells.

Voltage-gated potassium channels (Kv)—Kvs are on the plasma membrane that plays an important role for returning the depolarized cell to a resting state during action potentials.

By reconstituting responses seen in *Xenopus oocytes*, two separate groups showed that Sig-1Rs regulate voltage-gated potassium channels Kv1.3 and Kv1.4. Aydar and colleagues [39] demonstrated a functional interaction between the Sig-1R and Kv1.4 in the absence of ligands. A decade later, Kinoshita et al [40] revealed that Sig-1R interacts at the transmembrane domain of the Kv1.3 channels and alters their kinetics. In contrast to the study led by Aydar et al., Kinoshita and colleagues claimed that Sig-1R ligands are not required to alter (or block) the interactions between Kv1.3 channels and the Sig-1R. The interactions and dynamics of Sig-1R with the voltage gated potassium channel Kv1.2 were later identified and established in the animal model. In this report, cocaine exposure induces Sig-1R translocation to the plasma membrane and shapes intrinsic plasticity via the persistent association of Sig-1R and Kv1.2 in the nucleus accumbens shell medium spiny neuron [41]. Additionally, a recent study using confocal imaging revealed the colocalization of Sig-1R and Kv2.1 channel in the C-terminals of motor neurons [21]. The relationship between the Sig-1R and other ion channels were extended to a cardiac voltage-gated potassium channel hERG (human either-à-gogo related gene). The study was carried out in the leukemic K562 cell line to explore the potential pharmacological targets to reduce cancer progression. Electrophysiological data shows that the Sig-1R modulates the hERG current density in the presence of ligands [42]. Biochemical approaches including the co-immunoprecipitation study suggest that the Sig-1R expression potentiates the hERG subunit's ER/Golgi translocation and maturation [42]. Atomic force imaging and homogenous time-resolved fluorescence approaches later identified that the Sig-1R interacts with hERG with a four-fold symmetry. The authors clarify that the direct interaction between the Sig-1R and hERG in the plasma membrane is not Sig-1R ligand-dependent but is reduced by cholesterol depletion, suggesting that Sig-1R may bind to hERG in the ER and facilitate hERG assembly and trafficking perhaps in a lipid-raft related fashion [43]. The findings of the Sig-1R interacting with hERG in the ER and potentiating hERG maturation and translocation to the plasma membrane suggest that the Sig-1R may exert chaperoning activities in the ER to facilitate proper protein sorting to their final destinations. Thus, this relationship between the Sig-1R and hERG may apply to other Sig-1R-interacting partners as well.

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Voltage-gated sodium channels (Nav)—Nav on the plasma membrane are responsible for action potential initiation and propagation in excitable cells including nerve, muscle, and neuroendocrine cells.

The Sig-1R has been reported to modulate several sodium channels including Nav1.2, Nav1.4 and Nav1.5 [44–46]. Those studies investigated the modulation of the voltage-gated sodium channels by the Sig-1R by using various Sig-1R ligands. Results indicate that Sig-1R agonists exert inhibitory action on the Na^+ current that was in turn blocked by the Sig-1R antagonist progesterone [47]. The atomic force microscopy imaging of the co-isolated Sig-1R and Nav1.5 demonstrated that the Sig-1R binds to Nav1.5 with a 4-fold symmetry [44].

Notes on the interaction of the Sig-1R with proteins at the plasma membrane: Increasing reports are adding to the list of the ER Sig-1R chaperone associating partners. While the majority of the findings are based on the assumption that Sig-1R forms physical interactions with these proteins and regulates their activities at the plasma membrane, one needs to note that, due to the lack of a high-affinity Sig-1R antibody as well as the interfering signal from the control IgG which has the same molecular weight as the Sig-1R, immnuoprecipitation and the subsequent western blotting of endogenous Sig-1Rs remains technically challenging. Thus, most of the studies were carried out in the overexpression system, in which Sig-1Rs are expressed together with tagged proteins and are thus usually over-saturated in the cellular compartments that may lead to aberrant protein localizations. Therefore, it is conceivable that the over-expressed tagged Sig-1Rs may associate with some proteins that the endogenous Sig-1R may not associate with. Further, the electron microscopy study by Mavlyutov and coworkers demonstrated that the Sig-1R indeed could be localized in the proximity of plasma membrane. Thus, the Sig-1R may interact with the plasma membrane proteins via Sig-1R's proximity to the plasma membrane. Finally, a recent report suggested that the Sig-1R activation inhibits store-operated Ca^{2+} (SOCE) entry effects in rat brain microvascular endothelial cells [48]. However, the physical interaction, if any, between the Sig-1R and the SOCE protein complex ORAI1 or STIM1 has yet to be established.

In the cytosol

Cell engulfment and motility domain (ELMOD)—ELMOD proteins are GTPase-activating proteins (GAPs) for the ADP Ribosylation Factors (ARFs) and ARF-likes (ARLs) and can bind to the activated form of the GTPase (e.g. GTP-ARFs) to speed up the rate of hydrolysis of GTP and consequently inactivate the associated signaling.

Distinct GTPases control a variety of cross-talk signaling pathways, which require specific regulators, guanine-nucleotide exchange factors (GEFs) and GAPs. Those GTPases coupled with and controlled by GEFs or GAPs can be activated or inhibited respectively depending on their roles in the signaling pathway. Thus, investigation of the specificities and binding partners of GEFs and GAPs is essential to the construction of integrated models of cell signaling. Ivanova *et al*. [49] reported that ELMOD proteins are GAPs for the ARF family with links to deafness. According to their results, the Sig-1R acts as a new effector of the

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GAP activity of ELMOD1–3 proteins because direct binding of Sig-1R to either ELMOD1 or ELMOD2 results in the loss of GAP activity. This observation opens up a new link between the Sig-1R and GTPase (see below).

Ras-related C3 botulinum toxin substrate (Rac)-GTPase (Rac-GTPase)—Rac-GTPase is a subfamily of the Ras homolog gene (Rho) family of GTPases and is known to regulate tumor-cell migration, dendritic growth, and dendritic spine maturation.

Tsai *et al*. discovered that the Sig-1R regulates neuritogenesis and spine maturation via a signaling pathway involving Rac1-GTPase and its regulator TIAM1 [50]. Recently, Natsvlishvili et *al*. [51] reported that, by using immunoprecipitation, the Sig-1R not only directly interacts with Rac1-GTPase, but also forms complexes with IP3R, BiP, and Bcl2, in the brain mitochondria. Interestingly, the ligand-specific assembly complex relies on the Sig-1R agonist/antagonist and the presence of GTP/GDP. The author concluded that the Sig-1R-induced Rac1 signaling would trigger mild oxidative stress and the mild oxidative stress impacts neuroplasticity as well as prevents apoptosis and autophagy.

At the ER-mitochondrion interface and mitochondria

Binding Immunoglobulin Protein (BiP)—BiP, also known as 78 kDa glucose-regulated protein or heat shock 70 kDa protein 5, is a constitutively expressed ER protein that functions as a molecular chaperone. Bip is involved in the folding, translocation and assembly of proteins. It was reported that the Sig-1R forms a Ca^{2+}-sensitive chaperone machinery with BiP under normal physiological conditions [7, 52]. However, the lowering of the local Ca^{2+} concentration such as the efflux of Ca^{2+} from IP3R causes the Sig-1R to dissociate from BiP. Further, independent from the effect of local Ca^{2+}, the Sig-1R agonist like cocaine or (+)pentazocine can also cause the dissociation of the Sig-1R from BiP [7, 13]. It is known that this action of the Sig-1R agonist causes the Sig-1R to translocate from the MAM to the plasma membrane and nucleus.

Inositol 1,4,5- trisphosphate receptor type 3 (IP3R3), Ankyrin—In general, the IP3R plays an important role in the generation, propagation and regulation of cytoplasmic Ca^{2+} signals that regulate numerous physiological and pathophysiological processes. The IP3R3, a subtype of IP3Rs localizes mainly at the MAM and when activated by its agonist IP3 allows Ca^{2+} to efflux from the ER into mitochondria. However, after allowing for the Ca^{2+} efflux, IP3Rs' conformation is altered and is subjected to proteasomal degradation. The IP3R's degradation posed a question that puzzled researchers for many years: How does a cell restore the conformation of IP3R3 to ensure the proper Ca^{2+} signaling from the ER into mitochondria? The answer is: nature has provided the Sig-1R to come to rescue.

After dissociating from BiP, as stated above, the Sig-1R begins to bind IP3R3 at the MAM and chaperone IP3R3 [7]. As such, the Sig-1R ensures proper Ca^{2+} efflux from the ER into mitochondria via IP3R3 at the MAM and sustains/enhances cellular survival. Interestingly, it was demonstrated by Boehning *et al*. [8] that cytochrome c can bind IP3R3 and regulate Ca^{2+} signaling. Therefore, the possibility exists that the trimeric complex of Sig-1R-IP3R3-cytochrome c may play an important role in the homeostatic regulation of ER-mitochondrion Ca^{2+} signaling.

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Ankyrin, a family of cytoskeletal adaptor proteins, has been known to inhibit Ca^{2+} efflux from intracellular organelles by interacting with IP3Rs at the ER [53]. It was demonstrated that the Sig-1R agonist can cause the dissociation of ankyrin from the IP3R to open up the IP3R for Ca^{2+} efflux from the ER into the cytosol [54]. However, the exact relationship among the Sig-1R-BiP-ankyrin-IP3R remains to be totally clarified.

Voltage-dependent Anion Channels (VDAC)—VDAC localizes at the outer mitochondrial membrane (OMM) and forms a complex with IP3R that resides at the ER. The VDAC-IP3R complex facilitates transfer of Ca^{2+} from the ER to mitochondria.

Marriott *et al*. [55] reported that the Sig-1R can interact with VDAC and contributes to the regulation of mitochondrial pregnenolone synthesis. Studies have shown that the VDAC on the outer mitochondrial membrane may interact with steroidogenic acute regulatory protein [56], another exclusive outer mitochondrial membrane protein, and enhances the cholesterol import. The first report also revealed that deletion of Sig-1R disrupts the bridge formed via the Sig-1R association with VDAC2, resulting in an inhibition of cholesterol influx into the mitochondria. This Sig-1R-VDAC interaction may play an even more important role in the ER-mitochondrion cross-talk that has yet to be totally clarified. Further, it may be possible that this Sig-1R-VDAC interaction is partly responsible for maintaining the integrity of the MAM. In fact, losing the integrity of the MAM by the Sig-1R knockdown has been speculated to relate to the Alzheimer's disease [57].

Inositol-requiring enzyme 1 (IRE1)—IRE1 is an ER stress sensor that can splice the messenger RNA (mRNA) of X-box binding protein 1 (XBP1) to allow for expression of functionally active transcription factor XBP1 that in turn translocate into nucleus to induce the upregulation of several ER chaperones and antioxidant proteins or enzymes.

The ER provides an exclusive environment for protein synthesis and folding, which is vital to the cellular function. Under normal conditions, the synthesis and degradation of proteins remain in balance. Yet, numerous external insults could break the balance, causing the accumulation of undegraded or misfolded proteins. Thus, cells rely on a system, the unfolded protein response, which regulates the homeostasis of the ER by signaling the protein-handling problem to the nucleus via three ER stress sensors: IRE1, PERK, and ATF6. Mori *et al*. reported [10] that IRE1, but not PERK or ATF6, resides mainly at the MAM and that the mitochondria-derived ROS can preferentially activate IRE1 at the MAM. Further, the Sig-1R interacts only with IRE1 and not PERK or ATF6. The Sig-1R can thus stabilize IRE-1 to ensure a proper mitochondrion-ER-nucleus signaling axis for cellular survival by eventually prolonging the activation of the IRE1-XBP1 signaling pathway.

Insulin-induced gene (Insig)—Insig is an ER protein that plays an important role in the ER control of the cholesterol and lipid homeostasis by affecting the degradation of lipid-synthesizing enzymes via the ER-associated degradation system (ERAD).

Sig-1R plays a key role in oligodendrocyte differentiation by facilitating degradation of the enzyme Ceremide galatosyl transferase (CGalT, which synthesizes galactosylceremide to negatively affect oligodendrocyte differentiation [58]. The Sig-1R does so by forming a

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complex with Insig at the ER that is part of the ERAD that degrades the CGalT enzyme [58]. The Sig-1R agonist promotes the formation of the Sig-1R-Insig complex presumably to increase the degradation of CGalT to reduce the production of the negative regulator galactosylceramide. This study suggests that the Sig-1R is an important member of the ERAD system that degrades misfolded proteins immediately outside of the ER.

At the Nuclear Envelope: Emerin

The nuclear envelope consists of the outer nuclear membranes and the inner nuclear membranes. It is a highly organized dynamic barrier that separates the nucleus from the cytosol. It is known that the ER and nuclear envelope form a continuous network since both the inner and outer nuclear membranes are contiguous lipids from rough ER membrane. Dussossoy *et al*. [59] first reported the colocalization of the Sig-1R and sterol isomerase at the nuclear envelope and the ER. In the Sig-1R-EYFP overexpressing NG108 cells, Sig-1R agonists caused the Sig-1R to translocate toward the nuclear envelope and to the tip of the neurite [60]. Recently, an electron microscopy study revealed the precise subcellular distribution of Sig-1R in retinal neurons [14]. The study confirms that Sig-1Rs are localized in the inner and outer membrane of the nuclear envelope. These observations led to the important discovery that the Sig-1R is a transcriptional regulator at the nuclear envelope. Tsai and Chuang et al [15] discovered that the Sig-1R translocates from the ER to the outer nuclear membrane and interacts with the inner nuclear membrane protein emerin and likely the nuclear pore complex protein Ran-binding protein2 (RanBP2). Confocal imaging and coimmunostaining examinations demonstrated the interaction of Sig-1R and emerin at the nuclear envelope and the subsequent recruitment of barrier-to-autointegration factor, histone deacetylase 2, and the specific transcription factor 3 to the promoter of the monoamine oxidase B (MAOB) to suppress the gene transcription of MAOB. Cocaine acts as the Sig-1R agonist to intensify the complex formation. This finding opens a new chapter on how cocaine or other drugs may change the drug reward system. It is a widely accepted concept that cocaine and other drugs, such as methamphetamine, alter the DA levels in the synaptic cleft by blocking the DA reuptake and hijacking the brain reward system. This latest report demonstrating that cocaine, via the Sig-1R, is able to reduce the MAOB level in the NAc in a dopamine transporter-independent manner provides a new mechanism to understand the complexity of addictive processes.

Sig-1R–interacting proteins from bioinformatics (figure 2)

Proteomic and bioinformatics analyses have become important methods to predict potential protein-protein interactions. Many bioinformatics methods have been developed using different data mining routes and criteria (e.g., [61–63]). We looked into their respective web sites from those studies and chose to use one from the study by Schmitt et al ((funcoup.sbc.su.se) [61]) to look for predicted Sig-1R–interacting proteins partly because the confidence level of each predicted protein was easily accessed. We arbitrarily chose a confidence level of 0.948 for potential candidates because one of nuclear proteins of our interest was at this confidence level.

The predicted Sig-1R-interacting proteins in human are (in alphabetic order): AUP1 (ancient ubiquitous protein 1), C14orf1 (chromosome 14 open reading frame 1), CYC1 (cytochrome

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c-1), CYP51A1 (cytochrome P450, family 51, subfamily A, polypeptide 1), EIF5A (eukaryotic translation initiation factor 5A), GANAB (glucosidase, alpha; neutral AB), HSD17B12 (hydroxysteroid (17-beta) dehydrogenase 12), HSPA5 (heat shock 70kDa protein 5; glucose-regulated protein, 78kDa; BIP), LBR (lamin B receptor), NACA2 (nascent polypeptide-associated complex alpha subunit 2), NSDHL (NAD(P) dependent steroid dehydrogenase-like), NUP205 (nucleoporin 205kDa), PHB (prohibitin), PDZD11 (PDZ domain containing 11), RAE1 (RAE1 RNA export 1 homolog), RDH11 (retinol dehydrogenase 11 (all-trans/9-cis/11-cis)), RPS27A (ribosomal protein S27a), RPN2 (ribophorin II), SC4MOL (sterol-C4-methyl oxidase-like), SEC61A2 (Sec61 alpha 2 subunit (S. cerevisiae)), SLC25A11 (solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11), SLC25A39 (solute carrier family 25, member 39), SQLE (squalene epoxidase), SURF4 (surfeit 4), TM7SF2 (transmembrane 7 superfamily member 2), UBA52 (ubiquitin A-52 residue ribosomal protein fusion product 1), UBC (ubiquitin C), VDAC2 (voltage-dependent anion channel 2), XPO1 (exportin 1 (CRM1 homolog, yeast)), XPOT (exportin, tRNA (nuclear export receptor for tRNAs)).

The information from bioinformatics provides insight toward the potential proteins that may interact with the Sig-1R in theory. However, more experimental evidence is certainly needed to validate these results. For example, only two (HSPA5/BiP and VDAC2) of 22 Sig-1R-interacting proteins in figure 1 are correctly predicted by the bioinformatic means to be high-potential interactors at the confidence level of 0.948. The other 19 proteins in figure 1 are not predicted as potential interactors even at the confidence level of 0.30 except for the mouse Rac1 which has a confidence level 0.302. On the contrary, a predicted high-potential interactor (LBR: lamin B receptor) did not co-immunoprecipitate with the Sig-1R in an experiment [64]. In addition, a low-potential protein below a confidence level of 0.30, the lamin A receptor, was shown to co-immunoprecipitate with the Sig-1R [64]. This pattern of discordance between the experimental result and bioinformatic prediction concerning the Sig-1R interactors applies to those in human, mouse, or rat. Discordance of similar patterns was also found when searching the potential Sig-1R interactors by using tools from other two reports [62, 63].

The above discordance notwithstanding, it is important to point out that the predicted Sig-1R's interactors from bioinformatics may in fact be indirect "functional interactors" and not direct physical interactors. Further, many of the high-potential interactors from bioinformatic predictions have not been tested in the co-immunoprecipitation or other proximity assessment assays. The discordance as stated above may be reconciled in future studies.

CNS diseases reported to associate with the Sig-1R: speculation on the role of the Sig-1R in complex with respective interacting protein partner

The Sig-1R has been reported to be involved with certain CNS diseases (Table 1). Although the exact Sig-1R-interacting protein(s) which may relate to each disease is not totally clear at present, we tentatively place those proteins in the table simply to indicate the possibility as such. Nevertheless, the potential roles of the Sig-1R in interaction with its respective partners in some CNS diseases are speculated as follows.

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Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease)

The loss of function of Sig-1Rs in the motor neuron disrupted the ER-mitochondrion contact, caused a reduction of Ca^{2+} signaling, and stunned the axon extension, leading to amyotrophic lateral sclerosis in animals [65]. Thus, the action of Sig-1R–IP3R–VDAC in maintaining an intact contact between ER and mitochondria may play an important role in this disease. Further, the close proximity of the Sig-1R to the muscarinic acetylcholine receptor at the plasma membrane [21] may also be involved in this disease. In addition, the Sig-1R-Insig interaction may participate in the etiology of this disease because Insig was reported to be important in this disease by reducing the glutamate-induced excitotoxicity [66].

Alzheimers' disease

The Sig-1R plays an important role in maintaining the structural integrity of the MAM presumably through the tethering of the Sig-1R with IP3R and VDAC. The ER-mitochondrion cross-talk via the Sig-1R-IP3R-VDAC linkage at the MAM has recently been implicated to play an important role in the pathogenesis of Alzheimer's disease [57]. Knockdown of Sig-1R caused neurodegeneration. The level of Sig-1Rs is reduced in the brain of human Alzheimer's patients [57]. In addition, the Sig-1R-Insig interaction may play a role in this disease because Insig has been shown to be involved in the progress of the disease as it affects the cholesterol synthesis [67].

Huntington's disease

The "dopamine system stabilizer" class of drugs [68] have been suggested as potential agents to treat Huntington's disease as the drug can act as either a functional agonist or a functional antagonist depending on the initial levels of dopamine. One of those drugs is 4-[3-(methylsulfonyl)phenyl]-1-propylpiperidine (pridopidine) . Pridopidine, in addition to binding to dopamine D2R, binds the Sig-1R with an affinity 20 times higher than that at D2R in a PET imaging study [69], suggesting that pridopidine may work through its duel actions at D2R and Sig-1R [69]. As the Sig-1R has been shown to interact directly with D2R [20], it is tempting to speculate that the Sig-1R-D2R interaction may play an important role in the action of pridopidine. The effect of pridopidine against Huntington's disease may involve the drug's ability, like cocaine does [15], to translocate Sig-1Rs to the nuclear envelope to recruit chromatin-remodeling factors to suppress the gene expression of MAOB, thus increasing dopamine level in the brain. This possibility remains to be tested in the future.

Pain or neuropathic pain

The Sig-1R *per se* or its agonists was demonstrated to be involved in the attenuation of morphine-induced analgesia [25–27]. These results suggest the Sig-1R as an endogenous pain modulator in the CNS. Although the exact molecular mechanism remains to be totally clarified, the Sig-1R was shown to co-immunoprecipitate with the MOR in HEK cells [27]. Further, as stated above, the Sig-1R also co-immunoprecipitates with the NMDA receptor subunit GluN2 [32] as well as with CB1R [33], both of which are known to be involved in pain perception. Thus, the Sig-1R antagonists combined with morphine are being developed

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as an analgesic agent to reduce the dose of morphine while still maintaining effective analgesia.

Parkinson's disease

A Sig-1R agonist PRE-084 was found to induce functional neurorestoration in experimental Parkinsonism in that density of dopaminergic fibres is increased and a modest recovery of dopamine level is seen [70]. Further, this agonist treatment also causes a wider intracellular distribution of Sig-1Rs [70], presumably due to the agonist-induced Sig-1R translocation. As such, although the Sig-1R-interacting partner protein was not identified in this report, it is tempting to speculate that the Sig-1R agonist PRE-084 may cause the translocation of Sig-1Rs to the nuclear envelope to bind emerin which in turn recruits chromatin-remodeling factors to suppress the gene expression of MAOB [64], thus reducing the dopamine degradation and causing an increase of dopamine in the brain. However, another possibility for the involvement of the Sig-1R in this disease is that the Sig-1R can interact directly with TrKB [36] to enhance the receptor binding and/or signaling of the BDNF that is known to promote the survival of neurons.

Depression

BDNF, a neurotrophic factor, is known to play an important role in the action against depression because BDNF causes increases of dendritic spines and axon elongation for enhanced communications between neurons [71, 72]. BDNF does so via its receptor TrkB at the plasma membrane. The Sig-1R has been shown to be involved in depression partly through the Sig-1R's action in stabilizing the post-translational processing of mature BDNF [35]. Interestingly, the Sig-1Rwas also shown to co-immunoprecipitate with TrkB [36], suggesting that one of the antidepressive actions of the Sig-1R may be due to its ability to bind the BDNF receptor TrKB and enhance thereof the downstream signaling of TrkB.

Cocaine addiction

The Sig-1R-Kv1.2 interaction has been shown to shape neuronal and behavioral responses to cocaine [41]. This study demonstrated that cocaine "hijacks" Sig-1R to increase the interaction between Sig-1R and Kv1.2 potassium channel to decrease the intrinsic excitability of GABAergic neurons, thus leading to cocaine-induced behavioral sensitization. In addition, cocaine also causes the translocation of Sig-1R from the ER to the nuclear envelope to interact with emerin to suppress the gene transcription of dopamine-metabolizing enzyme MAOB to facilitate the action of cocaine [64].

Concluding Remarks

Thus, because the Sig-1R represents a new type of functional protein in the living system in that it can bind and modulate many different classes of functional proteins in many parts of the cell, we suggest to call the Sig-1R a pluripotent modulator (see Outstanding Questions box). It is perhaps because of this unique action of the Sig-1R that the receptor is involved in affecting or regulating so many different physiological and pathological conditions.

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At the MAM, the interaction between the Sig-1R and other proteins apparently encompasses functional sequelae for cellular survival because the Sig-1R: (1) Chaperones client proteins to maintain proper Ca^{2+} signaling from ER into mitochondria to ensure mitochondrial ATP production for bioenergetics; (2) Attenuates free radical generation by ensuring proper mitochondrion-ER-nucleus signaling; (3) Maintains the structural integrity of the contact between ER and mitochondria to facilitate the functional cross-talk of these two critical organelles; (4) Serves as a member of the ER-associated degradation system to regulate homeostasis of functional proteins; (5) Serves as the carrier of signaling lipid, specifically myristic acid [73], for proper functionality of neurons.

Outside of the MAM, the functional sequelae of the Sig-1R-target protein interaction may not be involved in cellular survival but in general relates to positive or negative modulation of the function of the target protein as indicated in the main portion of this opinion.

Although we have speculated above the potential role of the Sig-1R-target protein interaction in certain CNS diseases, questions in this regard remain: (1) What is the molecular basis of signaling that may relate the disease, in particular neurodegenerative diseases, to the Sig-1R at the MAM? If a functionally aberrant protein causes a disease, how does the cell signal the aberrance of that protein to the Sig-1R at the MAM? (2) If the disease for some reason causes the Sig-1R to translocate from the MAM, does the Sig-1R translocate to all other parts of the cell where the Sig-1R has been described? (3) Does the Sig-1R affect only the dysfunctional proteins? Does the Sig-1R do anything to a functionally normal protein? (4) Does the Sig-1R regulate the function of the interacting protein partner only by chaperoning the partner's conformation or by other as-yet-unknown actions?

Several questions also remain concerning the Sig-1R-related therapeutic agents for disease treatment: (1) Sig-1R agonists that may be effective in treating certain neurodegenerative diseases may also cause the Sig-1R to translocate from the MAM. What would the consequence be in terms of treatmetnefficacy? (2) Does the Sig-1R agonist continue to bind the Sig-1R after causing the translocation of the Sig-1R from the MAM? (3) What is the action of the Sig-1R agonist if it is translocated together with the Sig-1R to for example, the plasma membrane? Does the agonist serve to enhance the chaperone activity or other as yet unknown activity of the Sig-1R at the destined location? (4) Can the Sig-1R antagonist block the action of the Sig-1R even after the Sig-1R form a complex with target protein at the plasma membrane or nuclear envelope? (5) In the case of the hERG to which the Sig-1R binds at the ER and then co-translocates to the plasma membrane, how do we design drugs to facilitate or break up the interaction at the desired loci in a cell?

The reason why the Sig-1R can interact with so many structurally diverse proteins can only be speculated at present. Although numbers of chaperone proteins in the living system are limited, those chaperones have to maintain or help degrade thousands of other proteins. Thus, it is understandable that a chaperone has to interact and chaperone with many client proteins. So is the Sig-1R. However, the Sig-1R differs from other chaperones in that the Sig-1R has two transmembrane regions whereas none of other chaperones, as far as we know, has a transmembrane region. A particularly interesting question concerning the Sig-1R having two transmembrane regions is whether the transmembrane regions play any

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unique role in the action of the Sig-1R as a chaperone. This question deserves to be answered in the future in the light that most of the Sig-1R-interacting proteins are transmembrane proteins. Also, the Sig-1R differs from other chaperones in that while most of the action of other chaperones requires ATP, the Sig-1R does not require ATP in chaperoning the target protein [7].

Resent publications reporting the existence of Sig-1Rs in equilibrium as monomers, dimers and higher oligomeric forms may provide some answers, at least in part, as to why Sig-1Rs may bind so many target proteins or even ligands [74] [75] [13]. The formation of oligomers does not involve disulfide bonds. The Sig-1R agonist seems to favor monomers and dimers while the antagonist favors oligomers. Interestingly, certain ligands abolished the monomeric Sig-1R interactions with the plasma membrane ion channels. Thus, the ligand-gated oligomer/monomer equilibrium state of Sig-1Rs may attribute to Sig-1Rs being able to bind many different classes of ligands, target diverse proteins, and exert different chaperoning activities [13] [74, 75].

Whether the Sig-1R is the only member in this newly termed “pluripotent modulator” remains to be totally clarified in the future. Also unknown is the exact relationship between the ligand-induced oligomerization of Sig-1Rs and all of the actions of Sig-1Rs described above including these in the disease states. More investigations are certainly warranted to advance our understanding on this unique pluripotent modulator protein.

Lastly, although the Sig-2R has not been cloned, it is not reasonable to speculate that the Sig-2R could also be a chaperone with however potentially different interacting partners from those of the Sig-1R. This speculation is made because many studies so far have reported close and overlapping pharmacological and biochemical properties between the Sig-1R and Sig-2R.

Acknowledgments

This work is supported by the Intramural Research Program of the National Institute on Drug Abuse. Tzu-Chieh Su is supported in part by the Dragon Gate Program of the Ministry of Science and Technology of Taiwan (MOST #105-2911-I-038 -503). Yoki Nakamura is supported in part by the Japanese Society for Promotion of Sciences.

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Box 1

The sigma-1 receptor (Sig-1R) exists at the endoplasmic reticulum(ER)-mitochondrion interface called the MAM where the Sig-1R promotes cellular survival by (1) ensuring Ca2+ signaling from the ER into mitochondria by chaperoning the IP3 receptor; (2) enhancing the ER to nucleus signaling for antioxidant power by chaperoning the ER stress sensor IRE1; and (3) attenuating free radical damage through the Nrf2 signaling.

The Sig-1R can also translocate, upon the stimulation by agonists, from the MAM to the plasma membrane where Sig-1Rs interact with and affect the function of many other receptors, ion channels, and kinases. The Sig-1R can also translocate to the nuclear envelope where Sig-1Rs recruit chromatin-remodeling factors to affect the transcriptional regulation of genes. In addition, Sig-1Rs have been reported to interact with many other membranous and soluble functional proteins in other parts of cell including cytosol. The Sig-1R may thus represent a pluripotent modulator in the living system.

The Sig-1R has been shown to relate to many diseases including Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Huntington's disease, stroke/ischemia, pain/neuropathic pain, certain psychiatric disorders, cocaine addiction, myocardial hypertension, and cancer. Inasmuch as the Sig-1R acts as a pluripotent modulator, the dysfunction of the Sig-1R may thus play a role in those diseases. Thus pharmacological or cellular engineering targeting the Sig-1R, the pluripotent modulator, may provide therapeutic opportunities to treat those diseases.

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Outstanding Questions

What is the structural basis that allows the sigma-1 receptor to be able to interact with so many different classes of proteins with diverse structure and functions?

Why would the nature design such a protein to exist in the living system?

Is the sigma-1 receptor the only protein with this unique pluripotent action or is there any other member of this kind which has yet to be discovered?

Are all of the actions of the sigma-1 receptor described in this article relating to the chaperone nature of the sigma-1 receptor or is it some other as yet unknown nature of the sigma-1 receptor?

Given that the sigma-1 receptor can interact with so many functional proteins in the living system, how can we design drugs to target the specific protein that the sigma-1 receptor interacts with without affecting other interacting proteins?

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Trends Box

- The sigma-1 receptor (Sig-1R) exists at the endoplasmic reticulum(ER)-mitochondrion interface called the MAM (mitochondrion-associated ER membrane), where the Sig-1R promotes cellular survival
- The Sig-1R can, upon the stimulation of agonists or stress, translocate to the plasma membrane to interact with ion channels, receptors, and kinases
- Experimental or bioinformatics studies have identified interactions between the Sig-1R and many other functional proteins in the plasma membrane, ER, mitochondria, and even the cytosol.
- CNS diseases have been reported to relate to the Sig-1R, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, stroke/ischemia, pain/neuropathic pain, and certain psychiatric disorders
- Pharmacological or cellular engineering targeting the Sig-1R may provide therapeutic opportunities to treat those diseases

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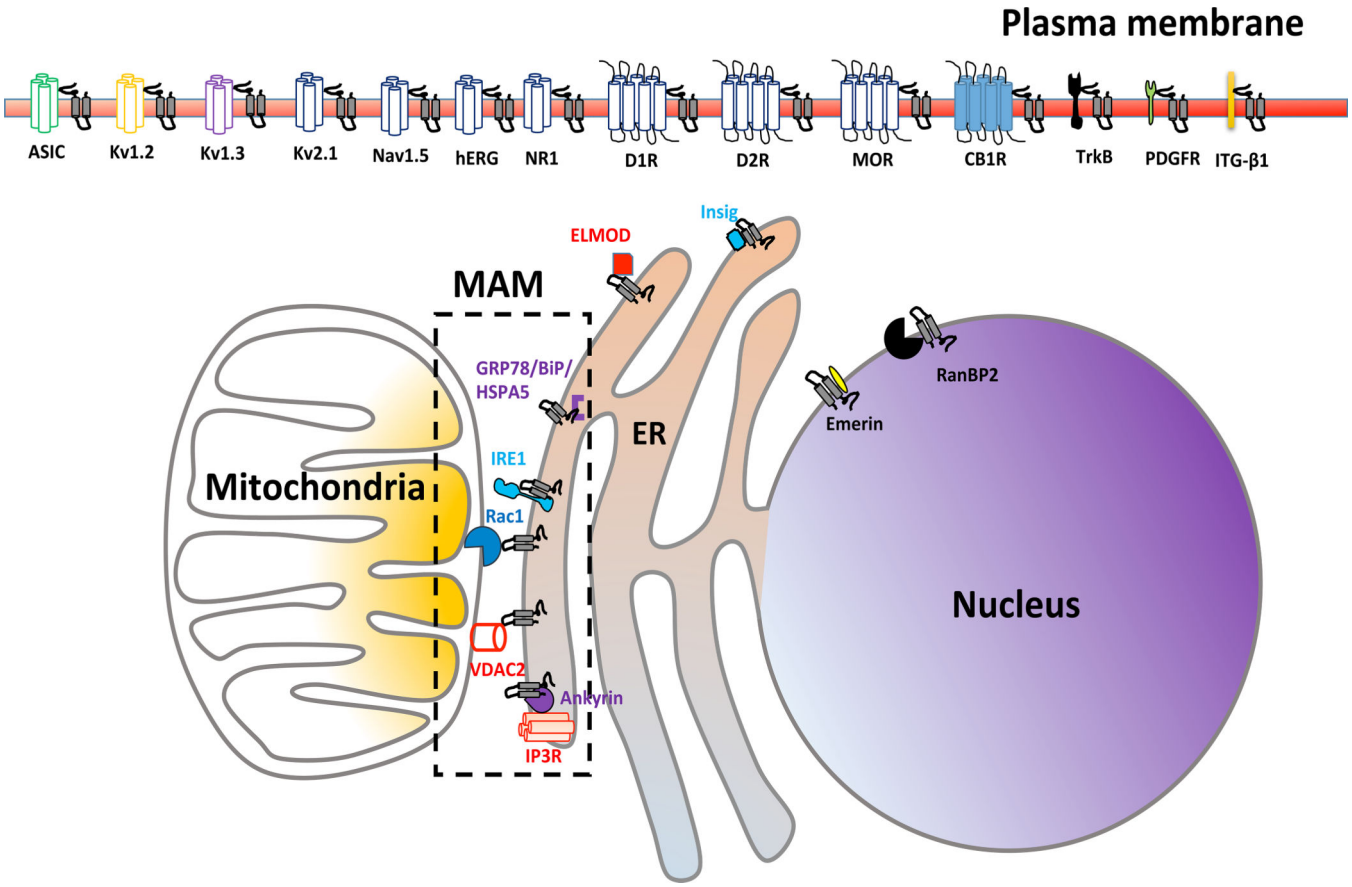

Figure 1. The sigma-1 receptor-interacting proteins as determined via experimental means

The sigma-1 receptor (Sig-1R) is shown as a two-transmembrane protein in black. ER, endoplasmic reticulum; MAM, the mitochondrion-associated ER membrane. Abbreviations for Sig-1R–interacting proteins are: (A) At the plasma membrane: ASIC, acid-sensing ion channel; Kv1.2, Kv1.3, and Kv2.1, voltage-gated potassium channel; Nav1.5, voltage-gated sodium channel; hERG, voltage-gated potassium channel hERG (human either-à-gogo related gene); NR1, NMDA receptor subunit 1; D1R, dopamine receptor 1; D2R, dopamine receptor 2; MOR, *mu* opioid receptor; CB1R, cannabinoid receptor 1; TrkB, Tropomyosin receptor kinase B for brain-derived neurotrophic factor; PDGFR, platelet-derived growth factor receptor. (B) In the cytosol, general endoplasmic reticulum membrane, or mitochondrial outer membrane: ELMOD, Cell engulfment and motility domain; Rac1, Ras-related C3 botulinum toxin substrate (Rac)-GTPase; Insig, insulin-induced gene. (C) At the endoplasmic reticulum-mitochondrion contact region called the MAM: GRP78/BiP/HSPA5, glucose response protein/immoprotein binding protein/heat shock protein A5; IRE1, inositol-requiring enzyme 1; VDAC, voltage-dependent anion channel 2; IP3R, inositol trisphosphate receptor. (D) At the nuclear envelope: RanBP2, Ran-binding protein2.

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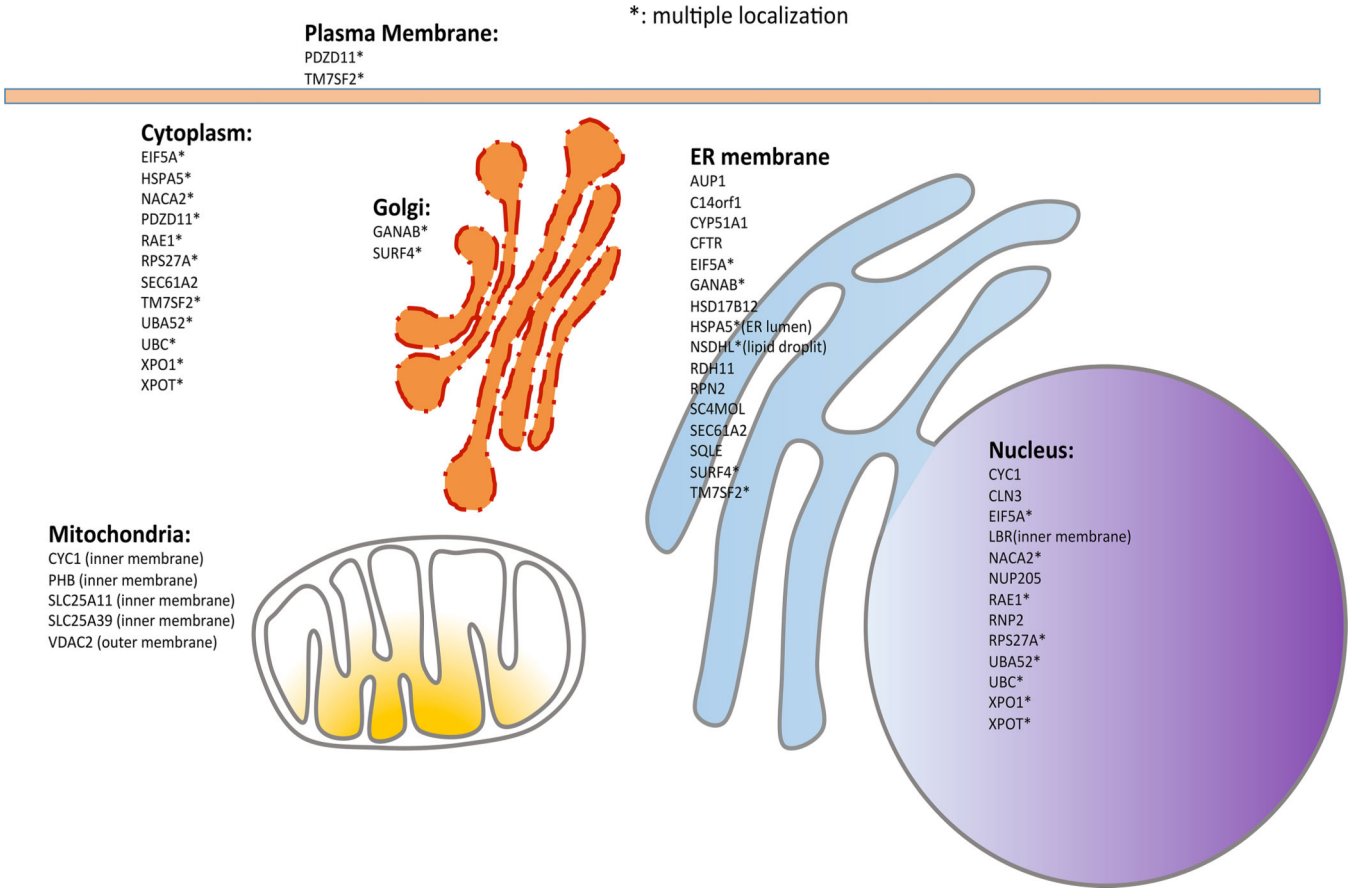

Figure 2. The proposed sigma-1 receptor-interacting proteins through a search created by one of the bioinformatics report [61]

Abbreviations (in alphabetic order) are: AUP1 (ancient ubiquitous protein 1), C14orf1 (chromosome 14 open reading frame 1), CYC1 (cytochrome c-1), CYP51A1 (cytochrome P450, family 51, subfamily A, polypeptide 1), EIF5A (eukaryotic translation initiation factor 5A), GANAB (glucosidase, alpha; neutral AB), HSD17B12 (hydroxysteroid (17-beta) dehydrogenase 12), HSPA5 (heat shock 70kDa protein 5; glucose-regulated protein, 78kDa; BIP), LBR (lamin B receptor), NACA2 (nascent polypeptide-associated complex alpha subunit 2), NSDHL (NAD(P) dependent steroid dehydrogenase-like), NUP205 (nucleoporin 205kDa), PHB (prohibitin), PDZD11 (PDZ domain containing 11), RAE1 (RAE1 RNA export 1 homolog), RDH11 (retinol dehydrogenase 11 (all-trans/9-cis/11-cis)), RPS27A (ribosomal protein S27a), RPN2 (ribophorin II), SC4MOL (sterol-C4-methyl oxidase-like), SEC61A2 (Sec61 alpha 2 subunit (S. cerevisiae)), SLC25A11 (solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11), SLC25A39 (solute carrier family 25, member 39), SQLE (squalene epoxidase), SURF4 (surfeit 4), TM7SF2 (transmembrane 7 superfamily member 2), UBA52 (ubiquitin A-52 residue ribosomal protein fusion product 1), UBC (ubiquitin C), VDAC2 (voltage-dependent anion channel 2), XPO1 (exportin 1 (CRM1 homolog, yeast)), XPOT (exportin, tRNA (nuclear export receptor for tRNAs)).

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TABLE 1

Sigma-1 receptor-associated CNS diseases

Disorders	Potential locations and interacting proteins	References
Amyotrophic Lateral Sclerosis (ALS)/Motor Neuron Disorders	BiP (ER) Insig (ER) RanBP2 (NE) mAchR (PM)	[75–88] [65, 66, 89–93]
Alzheimer's Disease (AD)	Rac-GTPase (mitochondria), BiP (ER and Mitochondria) IP_3R (MAM) Insig (ER)	[57, 67, 94, 95] [73, 96, 97]
HIV	PDGFR (PM)	[37, 98] [99–103]
Huntington's Disease (HD)	BiP (ER) D2R (PM) Emerin (NE)	[104] [105] [106] [69, 107]
Pain/Spinal Cord Injury	MOR (PM), NR1 (PM) CB1R (PM) TrKB (PM)	[25] [26, 27, 108] [109] [110] [111] [112] [113] [114] [115] [116] [117] [118] [119] [120] [121, 122]
Parkinson's Disease (PD)	TrKB (PM) Emerin (NE) IP_3R (MAM) Insig (ER)	[70, 123] [124]
Psychiatric Disorders (Schizophrenia and Depression)	BiP (ER) TrkB (PM) IP_3R (MAM)	[125] [126] [127] [128] [129] [130] [131] [132] [133] [134] [135] [36, 136]
Stroke and Ischemia	BiP (ER) IP_3R (MAM)	[137] [123, 138] [139] [140]
Traumatic Brain Injury (TBI)	BiP (ER) IP_3R (MAM)	[141]