

## REVIEW ARTICLE

# The Role of Sigma-1 Receptor, an Intracellular Chaperone in Neurodegenerative Diseases

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**Abstract: Background:** Widespread protein aggregation occurs in the living system under stress or during aging, owing to disturbance of endoplasmic reticulum (ER) proteostasis. Many neurodegenerative diseases may have a common mechanism: the failure of protein homeostasis. Perturbation of ER results in unfolded protein response (UPR). Prolonged chronic UPR may activate apoptotic pathways and cause cell death.

**Methods:** Research articles on Sigma-1 receptor were reviewed.

**Results:** ER is associated to mitochondria by the mitochondria-associated ER-membrane, MAM. The sigma-1 receptor (Sig-1R), a well-known ER-chaperone localizes in the MAM. It serves for Ca<sup>2+</sup>-signaling between the ER and mitochondria, involved in ion channel activities and especially important during neuronal differentiation. Sig-1R acts as central modulator in inter-organelle signaling. Sig-1R helps cell survival by attenuating ER-stress. According to sequence based predictions Sig-1R is a 223 amino acid protein with two transmembrane (2TM) domains. The X-ray structure of the Sig-1R [1] showed a membrane-bound trimeric assembly with one transmembrane (1TM) region. Despite the *in vitro* determined assembly, the results of *in vivo* studies are rather consistent with the 2TM structure. The receptor has unique and versatile pharmacological profile. Dimethyl tryptamine (DMT) and neuroactive steroids are endogenous ligands that activate Sig-1R. The receptor has a plethora of interacting client proteins. Sig-1R exists in oligomeric structures (dimer-trimer-octamer-multimer) and this fact may explain interaction with diverse proteins.

**Conclusion:** Sig-1R agonists have been used in the treatment of different neurodegenerative diseases, e.g. Alzheimer's and Parkinson's diseases (AD and PD) and amyotrophic lateral sclerosis. Utilization of Sig-1R agents early in AD and similar other diseases has remained an overlooked therapeutic opportunity.

**Keywords:** Neurodegenerative diseases, sigma-1 receptor, pharmacology, agonist, DMT, antagonist, chaperone.

## 1. INTRODUCTION: BRIEF HISTORY OF THE SIGMA-1 RECEPTOR

Neurodegenerative diseases (NDDs) are described as disorders with progressive loss of neuronal integrity, both structural and functional. Abnormal protein folding is widely believed to be coupled with neurodegeneration. Alzheimer's and Parkinson's disease (AD and PD) are the most common forms of NDDs; Lewy body disease (DLB), Huntington

disease (HD) and amyotrophic lateral sclerosis (ALS) are less frequent. Currently, only symptomatic treatments are available, which ameliorate the symptoms without halting or slowing the progression of disease. There is an urgent need to develop effective, disease modifying therapeutics to protect and restore neuronal integrity. The first step on this way is a better understanding of the pathomechanisms of NDDs for the selection of new drug targets. Among the putative targets for neuroprotection, recently the sigma-1 receptor (Sig-1R) has gained more and more attention.

The Sig-1R is an enigmatic protein with a unique amino acid sequence (homologous only to yeast sterol isomerases [2]), a unique pharmacological profile and a puzzling his-

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tory. Not long time ago, it has been classified as a member of the orphan receptors for which no endogenous ligand was known until the recent discovery of the endogenous hallucinogen DMT (N,N-dimethyltryptamine) as its endogenous agonist [3]. Today, the Sig-1R is considered to be a non-G-protein coupled, non-ionic intracellular chaperone at the endoplasmic reticulum (ER) that modulates Ca<sup>2+</sup>-signaling.

It has been a long way to arrive to this conclusion. The history of discovery of Sig-1R has existed for 40 years. Originally, Sig-1R was thought to be a member of the opioid receptor family. In 1976, Martin reported that the psychotomimetic effects of SKF-10,047 (N-allylnormetazocine) in chronic spinal dogs do not originate from the  $\mu$  and  $\kappa$  opioid receptors (named from the first letter of their selective ligands morphine and ketazocine, respectively). He proposed the introduction of a new type of the opioid receptors; sigma (from the first letter of SKF-10,047) [4]. This receptor was reported to be blocked by the universal opioid antagonist, naloxone. Later, Su identified a distinct binding site to mediate the psychotomimetic effect of SKF-10,047 that was, however, insensitive to naloxone and naltrexone [5]. Mistakenly, the binding site was named sigma/opioid receptor; then the name was changed to sigma receptor [6]. Sig-1R was also defined as an NMDA (N-methyl-D-aspartate) receptor because phencyclidine (PCP) binds to the sigma receptor and (+)SKF-10,047 to the PCP-site of the NMDA receptor [7]. Radioligand binding studies identified two populations of the sigma binding sites (Sig-1 and Sig-2) that differ in their ligand selectivity, tissue and subcellular distribution [8, 9]. In recent years, significant achievements have been made in our understanding of the molecular basis of the Sig-1 subtype in normal and pathological conditions. The sigma-2 subtype has remained more obscure due to the lack of suitable research tools (it has not yet been cloned). Sig-1 receptors (the original sigma receptors) display high (nanomolar) affinity for the 'unnatural' (+) stereoisomer of benzomorphans <https://en.wikipedia.org/wiki/Benzomorphan> (e.g. SKF-10,047, pentazocine) and only low to moderate affinities for (-) isomers. (+)-Pentazocine, the prototypic Sig-1R agonist binds with more than 100-fold selectivity to Sig-1 versus Sig-2 binding sites, while 1,3-di-o-tolylguanidine (DTG) binds nearly equally well at both populations [10]. DTG in the presence of (+) pentazocine (to mask Sig-1 binding) has been the ligand of choice to study the Sig-2 subtype. In this review, we will focus on the Sig-1R type. The pharmacology of the Sig-1R has been summarized in recent reviews [11-17].

## 2. THE UNIQUE PROPERTIES OF SIG-1R: CHAPERONE FUNCTION, DISTRIBUTION, SUBCELLULAR LOCALIZATION AND TRANSLOCATION

There are several properties of Sig-1R that make this protein unique among the receptors. The most important feature of Sig-1R: it is an intracellular receptor acting as a chaperone protein. The Sig-1R differs also structurally from the classical neurotransmitter receptors: although a transmembrane protein, it has only one transmembrane region [1]. (The results of *in vivo* studies are rather consistent with the 2 transmembrane structure of Sig-1R. Sig-1R shows no post-

natal ontogeny and age-dependent increase of receptor density [18]. These properties and the widespread modulatory functions of Sig-1R underline the universal role of Sig-1R in cellular functions and cell survival. Alternative splicing results in the canonical isoform (223 amino acids) and 4 other transcript variants (UniProt identifiers: Q99720-1 to Q99720-5) [19].

Sig-1R has very versatile cellular function. Interestingly, the Sig-1R knock-out mice are viable and fertile, and do not show any apparent phenotype changes except for a reduced hypermotility response compared to wild-type mice [20]. Through regulation of lipid rafts, secretases, kinases, neuroreceptors and ion channels, the Sig-1R can influence signal transduction, citric acid cycle, oxidative stress, neuronal plasticity, *etc.*

The central nervous system (CNS) appears to be the primary site of Sig-1R activity and effects. Sig-1Rs are broadly spread in the CNS (e.g. hippocampus: highest density in dentate gyrus; hypothalamus, mesencephalon, olfactory bulb), in peripheral (abundantly in liver, kidney, lung, muscle), endocrine, immune and reproductive tissues [21]. At the cellular level, the Sig-1Rs are expressed in neurons, oligodendrocytes and ependymocytes. They are primarily found at the ER membranes that are physically associated with the mitochondria (MAM: mitochondria-associated ER membrane) [22] and are mainly associated with neuronal perikarya and dendrites [21, 23, 24].

It is also unique that Sig-1R is a transmembrane protein which can dynamically translocate inside cells. Sig-1R localizes mainly at the MAM in ceramide-enriched microdomains, apparently bound to ceramide [25]. Sig-1R also binds the binding immunoglobulin protein (BiP), another ER-chaperone that prevents the translocation of Sig-1R [23]. Translocation of Sig-1Rs from the ER to the plasma membrane (PM) has been reported [26], where Sig-1R interacts with many receptors, ion channels and kinases. Translocation occurs after stimulation of Sig-1R by agonists like cocaine: the receptor can dissociate from BiP and translocate to the PM, the nuclear envelope and can interact with cytosol proteins [27].

## 3. STRUCTURAL FEATURES OF THE SIG-1R

The heterogeneity of the sigma receptors and the lack of selective sigma ligands have greatly contributed to the difficulties of the classification of this receptor type. The controversy of the nature of sigma receptors was finally solved in 1996 by the successful cloning of the Sig-1R gene from guinea pig liver [28]. It was demonstrated that the Sig-1R consists of 223 amino acids hypothetically with two putative transmembrane domains (TMDs) [29, 30]. The Sig-1R shares no sequence homology with any mammalian protein. However, it shares 60% amino acid identity to a yeast sterol isomerase, ERG2, although the mammalian Sig-1R does not have any enzyme activity [2, 31]. Subsequent cloning studies from a variety of tissues found 90% sequence conservation in mammalian species [32, 33]. The gene that encodes the human Sig-1R is located on chromosome 9p13 and contains four exons and three introns [34]. Hydropathy analysis of the Sig-1R described three hydrophobic regions [35]. Sequence-

based algorithms that predict amino acid hydrophobicity (TMBase) have indicated two major hydrophobic helical transmembrane sequences (TMDI and TMDII) [29]. Former studies indicate that amino acid (AA) sequence 11-29 and 92-112 represent the TMDI and TMDII, respectively. It is proposed that AA 29-92 forms a cytosolic loop and both the C- and N-termini are localized in the ER lumen [23, 36, 37]. More recent predictions show that TMDI spans between AA 8 and 34, TMDII between AA 83 and 111 [38]. The Sig-1R orientation predicts that if the protein translocates into the plasma membrane, the C- and N-termini are located outside the cell. The so called steroid binding domain I and II (SBDL-I; SBDL-II) together with the TMDs and the C-terminus have been revealed to be essential for ligand binding [39-41]. (The SBDL regions are thus named because of sequence homology to yeast sterol isomerase.) Photolabeling studies of A. Pal, *et al.* suggest that SBDL-I and SBDL-II regions of Sig-1R may be involved in forming a Sig-1R ligand binding site [42]. The 50AA cytosolic loop between the TMDI and TMDII has been studied by NMR and proposed to contain 3 short helical regions [38]. A model of the key structural motifs of Sig-1R was published by Ortega-Roland as well as U.B. Chu and A.E. Ruoho [43]. An excellent review summarizes our present knowledge about the Sig-1R structure [44].

Very recently, the first crystal structure of the full-length human Sig-1R was reported in complex with two chemically divergent ligands, PD144418 (a high affinity and selective sigma-1 antagonist) and 4-IBP (agonist or inverse agonist) [1]. The structure reveals a triangular organization comprising three tightly associated protomers, each with a single transmembrane domain at the corner of a trimeric triangle. The C-terminal domain of the receptor shows an extensive, flat, hydrophobic membrane-proximal surface, the cytosolic surface is polar. Receptor binding would occur through a charge-charge interaction with the highly conserved Glu172, consistent with previous site-directed mutagenesis studies identifying this residue as essential for ligand binding [1, 45, 46]. However, this crystal structure of the Sig-1R was gained by an *in vitro* approach of embedding the receptor in lipid-containing nanodiscs. The discrepancy between the sequence-based prediction (two transmembrane) and X-ray (one transmembrane) structures suggests that the *in vitro* crystal structure not accurately represents the *in vivo* structure. The structure differences may indicate a potentially amorphous intrinsically disordered *in vivo* structure for the Sig-1R.

Previous biochemical and cellular studies suggest that oligomerization is a key functional property of this receptor and may be linked to ligand efficacy [1, 47, 48]. Sig-1R exists in rat liver membrane in oligomeric form [42]. Forster resonance energy transfer (FRET) analyses have shown that Sig-1R exists constitutively in monomeric and oligomeric (dimer-trimer-octamer-multimer) form [49]. Dimer and monomer forms of Sig-1R were favored in the presence of agonist (+)-pentazocine. Simultaneous studies demonstrated the presence of higher order oligomers favored by the Sig-1R antagonist haloperidol. A hypothetical mechanistic model of Sig-1R oligomerization proposes that agonists create functionally active dimers and/or monomers from higher

order oligomers [48]. Putative antagonists (or inverse agonists) shift the equilibrium to the tetramer/oligomer forms, and thus higher oligomers might represent a reservoir for the active form.

The receptor as a chaperone protein is able to accommodate many client proteins (Tables 2 and 3), and tolerates very different structure of binding clients. The C-terminal tail (amino acid sequence 110-123) possesses chaperone functions [23, 50]. The mystery, why Sig-1R has so many interacting proteins (Tables 2 and 3) can be dissolved with the activity of alternately spliced variants of Sig-1 R or the interaction oligomeric structures of the receptor with proteins. The hypothetical IDP character of Sig-1R might explain the receptor structure stabilization by trimerization (in membrane environment) and interactions with the co-chaperone BiP [38].

#### 4. SIG-1R AGONISTS, ANTAGONISTS AND ALLOSTERIC MODULATORS

An intriguing feature of the Sig-1R is that it binds ligands with very diverse structures. These include small molecules that also interact with other targets, such as haloperidol, dextrometorphan, metamphetamine, verapamil, chloroquine, fluoxetine, donepezil, *etc.* Specifically, a majority of antipsychotics possess high to moderate binding affinities to Sig-1R [51]. Based on extensive structure-activity relationship studies, Glennon *et al.* published a simple pharmacophore model for small molecule binding to the Sig-1R [52]. He postulated that the binding site consists of a basic amine site separated by two hydrophobic regions. The primary hydrophobic region is optimally an N-arylalkyl group and is situated at four-to six-carbons (6-10 Å), and a second hydrophobic domain 1- to 3-carbon apart (2.5-4 Å) from the obligate nitrogen. The unique hydrophobic nature of the ligand binding site enables hydrophobic moieties to associate with the binding site. Indeed, most Sig-1R ligands possess hydrophobic or amphipathic property (*e.g.*, haloperidol and fluvoxamine) and are positively charged. The neuroactive steroids (*e.g.* DHEA, progesterone), that induce several of their physiological effects through sigma receptors and are hypothesized to be endogenous ligands for them, were shown to bind with moderate to weak binding affinities at this site [6]. Interestingly, this steroid does not have a nitrogen atom. The endogenous ligand for the Sig-1R has not been unequivocally identified yet, but the endohallucinogen DMT and sphingosine have also been postulated [3, 6, 53].

The molecular basis of ligand efficacy is yet to be solved. Different methods are used in Sig-1R binding studies and no standard method of characterization has been chosen. The efficacy (agonist, antagonist) is not an absolute property of the ligand, it is influenced by the methods and tissues of the measurements. By convention, Sig-1R 'agonists' are those compounds that induce the typical Sig-1R effects in whole-animal physiologic studies or resemble the phenotypes of receptor overexpression. Selective Sig-1R agonists include: (+)-pentazocine, dehydroepiandrosterone, (+)-SKF10,047, PRE-084 (2-morpholin-4-ylethyl-1-phenyl- cyclohexane-1-carboxylate), and SA4503 (1-[2-(3,4-dimethoxyphenyl) ethyl]-4-(3-phenylpropyl)piperazine). 'Antagonists' are those compounds that generally have no effects on their own, but

attenuate the effects of Sig-1 stimulation or resemble the results of the gene knock-down. Sig-1R antagonists that are commonly cited in the literature include: progesterone, haloperidol, BD1047 (N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino) ethylamine), BD1063 (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine), and NE-100 (4-methoxy-3-(2-phenylethoxy)-N,N-dipropylbenzeneethanamine). The involvement of the Sig-1 subtype in a given system requires careful analysis and verification using selective genetic and pharmacological tools. Several known drugs (*e.g.* SKF 83959, an atypical dopamine receptor-1 agonist) potentiate the binding of (+)-pentazocine to Sig-1R by allosteric manner [54]. SKF 83959 also inhibits microglia mediated inflammation [55]. SOMCL-668 (3-methyl-phenyl-2,3,4,5-tetrahydro-1H-benzo(d)azepin-7-ol), the latest identified novel and selective allosteric modulator of Sig-1R displays anti-seizure and antidepressant activity [54, 56].

A complete list of Sig-1R ligands is difficult to obtain, as many compounds only have been used in pharmaceutical research and are not available, due to drug development. A very useful summary of the pharmacological properties of Sig-1R ligands were published by E.J. Cobos *et al.* [57]. Table 1 shows the short list of the most important Sig-1R agonists, antagonists and allosteric modulators.

## 5. SIG-1R INTERACTIONS WITH PROTEINS AND LIPIDS. MECHANISMS OF ACTION

The chaperone activity and the specific 3D barrel structure [1] of Sig-1R may answer the question why the Sig-1R has so many client proteins. The lists of these proteins are given in Tables 2 and 3 [14, 58]. The Sig-1Rs have been shown to play a role in numerous phenomena including cardiovascular function, drug abuse, schizophrenia, clinical

**Table 1. A short list of Sig-1R ligands (agonists and antagonists).**

Agonists	Refs.	Other Activities
N,N-Dimethyltryptamine (DMT)	[3, 172, 173]	5HT2A receptor agonist
(+)-N-allylnormetazocine ((+)-SKF 10,047)	[51]	NMDA receptor ligand
2-(4-morpholino)ethyl-1-phenylcyclohexane-1-carboxylate (PRE-084)	[23, 174]	–
1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl) piperazine (SA 4503, cutamesine)	[175]	–
4-phenyl-1-(4-phenylbutyl)piperidine (PPBP)	[176]	nNOS inhibition
1-(2,8-Dimethyl-1-thia-3,8-diazaspiro(4,5)dec-3-yl)-3-(1H-indol-3-yl)propan-1-one (AF710B)	[123]	allosteric M1 agonist
Dehydroepiandrosterone (DHEA)	[177]	neurosteroid, nuclear receptors
Donepezil	[128, 178, 179]	cholinesterase inhibitor
Amitriptyline	[180]	neurotransmitter reuptake blocker
Fluvoxamine	[23, 36, 181, 182]	5HT reuptake inhibitor
Memantine	[183]	NMDAR antagonist
Ifenprodil	[184]	NMDAR antagonist, $\alpha$ -1 antagonist
(+)-Pentazocine	[23, 185, 186]	–
Cocaine	[23, 187]	neurotransmitter reuptake blocker
Dextromethorphan (DEX)	[30, 188]	NMDAR allosteric antagonist
<b>Antagonists</b>		
N-(2-(3,4-dichlorophenyl)-N-methyl-2-(dimethylamino)ethylamine (BD 1047)	[189]	$\beta$ -adrenoreceptor ligand
1-(2-(3,4-dichlorophenyl)ethyl)-4-methylpiperazine (BD 1063)	[189]	–
4-Methoxy-3-(2-phenylethoxy)-N,N-dipropylbenzeneethanamine (NE-100)	[23]	–
Progesterone	[23]	neurosteroid, progestogen
Haloperidol	[23]	D2 and D3 antagonist
Verapamil	[190]	Ca <sup>2+</sup> -antagonist, slow channel blocker
Sertraline	[60]	5HT reuptake inhibitor

**Table 2. Sig-1R interacting proteins (direct interactions) [14].**

<p><i>Plasma membrane proteins:</i></p> <ul style="list-style-type: none"> <li>▪ Acid-sensing ion channels (ASICs)</li> <li>▪ Dopamine receptors (D1R, D2R)</li> <li>▪ Muscarinic acetylcholine receptor (mAChR)</li> <li>▪ Mu-Opioid receptor (MoR)</li> <li>▪ NMDA receptor (subunit1)</li> <li>▪ Cannabinoid receptor1 (CB1R)</li> <li>▪ Tropomyosin receptor kinase B (Trk B)</li> <li>▪ Platelet-derived growth factor receptor (PDGFR)</li> <li>▪ Integrin-D1</li> <li>▪ Voltage-gated potassium channels (K<sub>v</sub>)</li> <li>▪ Voltage-gated sodium channels (Na<sub>v</sub>)</li> </ul>
<p><i>Cytosol proteins:</i></p> <ul style="list-style-type: none"> <li>▪ Cell engulfment and motility domain (ELMOD)</li> <li>▪ Ras-related C3 botulinum toxin substrate (Rac)-GTPase</li> </ul>
<p><i>ER-mitochondrion interface (MAM) and mitochondrial proteins</i></p> <ul style="list-style-type: none"> <li>▪ Binding immunoglobulin protein (BiP)</li> <li>▪ Inositol 1,4,5-triphosphate receptor Type 3 (IP<sub>3</sub>R<sub>3</sub>)</li> <li>▪ Ankyrin</li> <li>▪ Voltage-dependent anion channels (VDAC)</li> <li>▪ Inositol-requiring enzyme (IRE1)</li> <li>▪ Insulin-induced gene (Insig)</li> </ul>
<p><i>Nuclear envelope proteins</i></p> <ul style="list-style-type: none"> <li>▪ Emerin</li> <li>▪ Ran-binding protein (RanBP2)</li> </ul>

depression, cancer and modulate mood disorders, amnesic and cognitive deficits as well as potentiate analgesia [6, 11, 16, 59]. They are now considered as ligand-regulated molecular chaperones (for a review see [22, 60] of which the main physiological function is modulation of intracellular calcium signaling [23], inhibition of voltage-gated K<sup>+</sup> channels [13, 30, 61], and release of various neurotransmitters including acetylcholine and glutamate [62]. Sig-1R is intimately involved with the glutamate system and seems to be an essential part of the excitotoxicity. Sig-1R is implicated in cellular differentiation, neuroplasticity, neuroprotection and cognitive functioning of the brain [11, 63]. The signal transduction pathways of these phenomena have not been clarified yet. Sig-1 antagonists, but not agonists were shown to display GTP- and suramine sensitive high affinity binding implying coupling of the receptor to G-proteins [64]. Early radioligand binding studies showed that the binding of Sig-1 ligands was altered by GTP and its analogues [65]. Contrary, evidence was published that the Sig-1R is not coupled to G-proteins [66]. Sig-1R has a high tendency to form heterodimers with other proteins, *e.g.* receptors, ion channels. The recent crystallization studies of the Sig-1R did not find any structure similarity of Sig-1R to the 7 transmembrane GPCRs [1]. The Sig-1R appears in a complex with voltage gated K<sup>+</sup>-channels (K<sub>v</sub>1.4 and K<sub>v</sub>1.5), leading to the idea that these receptors are auxiliary subunits [61]. There is evidence

that Sig-1Rs are intracellular signal transduction amplifiers [67], regulators of inter-organelle communication [27, 68] or pluripotent modulators [14].

Sig-1R integrates many signaling pathways and in particular modulates Ca<sup>2+</sup> signaling through the inositol triphosphate (IP<sub>3</sub>) receptor between the ER and mitochondria [23]. Its participation is important in other ion channel and related receptor (K<sup>+</sup> channel, NMDA receptor) activities as well, in lipid transport and metabolism, especially during neuronal morphogenesis and differentiation. The ER-mitochondrion border at the MAM – where the Sig-1R resides – serves as an important subcellular interface in the regulation of cellular survival by enhancing the stress-response signaling [69]. Sig-1R protects the cells against reactive oxygen species (ROS) and activates the antioxidant response elements [70], therefore Sig-1R agonists may function as indirect antioxidants. The induction of Sig-1R can repress cell death signaling: up-regulation of Sig-1R suppresses the apoptosis caused by ER stress [71]. Tryptaminergic trace amines (like DMT) as well as neurosteroids (*e.g.* dehydroepiandrosterone, pregnenolon) are endogenous ligands that activate the Sig-1R [3] and are expected to elicit the described effects.

The ER chaperone function of the Sig-1R is essential for metabotropic receptor signaling and for survival against cellular (particularly ER) stress. Dysfunctional chaperones are

**Table 3. Proposed Sig-1R interacting proteins revealed by bioinformatics analyses [58].**

<i>Plasma membrane proteins</i>
<ul style="list-style-type: none"> <li>▪ PDZ-domain containing 11 (PDZD11)</li> <li>▪ Transmembrane 7 superfamily member 2 (TM7SF2)</li> </ul>
<i>Citoplasm proteins</i>
<ul style="list-style-type: none"> <li>▪ Eukaryotic translation initiation factor 5A (EIF5A)</li> <li>▪ Heat shock 70-kDa protein5 (HSPA5)</li> <li>▪ Nascent polypeptide-associated complex <math>\alpha</math>-subunit 2 (NACA2)</li> <li>▪ RNA export 1 homolog (RAE1)</li> <li>▪ Ribosomal protein S27a (RPS27A)</li> <li>▪ Sec61 <math>\alpha</math>-2 subunit (SEC61A2)</li> <li>▪ Ubiquitin A52 residue ribosomal protein fusion product1 (UBA52)</li> <li>▪ Ubiquitin C (UBC)</li> <li>▪ Exportin 1, CRM1 homolog (XP01)</li> <li>▪ Exportin (tRNA) (XPOT)</li> </ul>
<i>ER membrane</i>
<ul style="list-style-type: none"> <li>▪ Ancient ubiquitous protein1 (AUP1)</li> <li>▪ Chromosome 14 open reading frame (C14 orf1)</li> <li>▪ Cytochrom P450, family 51 (CYP51A1)</li> <li>▪ Eukaryotic translation initiation factor 5A (EIF5A)</li> <li>▪ Glucosidase, <math>\alpha</math>, neutral AB (GANAB)</li> <li>▪ Hydroxysteroid (17-<math>\beta</math>) dehydrogenase 12 (HSD17B12)</li> <li>▪ Nascent polypeptide-associated complex <math>\alpha</math>-subunit 2 (NACA2)</li> <li>▪ NAD(P) dependent steroid dehydrogenase-like (NSDHL)</li> <li>▪ Retinol dehydrogenase 11 (RDH11)</li> <li>▪ Ribophorin II (RPN2)</li> <li>▪ Sterol-C4-methyl oxidase like (SC4MOL)</li> <li>▪ Sec61 <math>\alpha</math>-2 subunit (SEC61A2)</li> <li>▪ Squalene epoxidase (SQLE)</li> <li>▪ Surfeit 4 (SURF4)</li> <li>▪ Transmembrane 7 superfamily member 2 (TM7SF2)</li> </ul>
<i>Mitochondria</i>
<ul style="list-style-type: none"> <li>▪ Cytochrome c-1 (inner membrane) (CYC1)</li> <li>▪ Prohibitin (inner membrane) (PHB)</li> <li>▪ Solute carrier family 25, member 39 (inner membrane) (SLC25A39)</li> <li>▪ Solute carrier family 25, member 11 (inner membrane) (SLC25A11)</li> <li>▪ Voltage dependent anion channel 2 (outer membrane) (VDAC2)</li> </ul>
<i>Nucleus</i>
<ul style="list-style-type: none"> <li>▪ Exportin 1 (XP01)</li> <li>▪ Exportin (tRNA) nuclear export receptor for tRNAs (XPOT)</li> <li>▪ Cytochrom c-1 (CYC1)</li> <li>▪ Eukaryotic translation initiation factor 5A (EIF5A)</li> <li>▪ Lamin B receptor (LBR)</li> <li>▪ Nascent polypeptide-associated complex <math>\alpha</math>-subunit 2 (NACA2)</li> <li>▪ Nucleoporin 205 kDa (NUP205)</li> <li>▪ RNA export 1 homolog (RAE1)</li> <li>▪ Ribosomal protein S27 (RPS27A)</li> <li>▪ Ubiquitin A52 residue ribosomal protein fusion product1 (UBA52)</li> <li>▪ Ubiquitin C (UBC)</li> </ul>

responsible for numerous diseases [72], especially the neurodegenerative ones. Sig-1R has so far been implicated in illnesses like AD [73, 74], PD [75], cancer [76], cardiac conditions [77] retinal dysfunction, perinatal and traumatic brain injury, ALS, HIV-related dementia, major depression, and psychostimulant addiction [78]. In addition, Sig-1R mutations have been implicated in frontotemporal lobar degeneration (FTLD) and ALS [79]. How Sig-1R may relate to this plethora of diseases remains to be clarified but its protective influence has been verified on various aspects of cellular processes, such as  $Ca^{2+}$  signaling, mitochondrial functions, ER stress, apoptotic pathways, and tumor cell proliferation [12]. As Sig-1Rs are expressed in the immune system, immunomodulatory functions have also been reported in the literature [80, 81]. Although the interaction of Sig-1R in different tissues is very complex, apparently Sig-1R plays a central role in neurotransmission and apoptosis. The development of new knockout mice and transgenic lines will facilitate further research.

## 6. SIG-1R AS A PLURIPOTENT MODULATOR IN CELLS

The ER-chaperone Sig-1R resides at the MAM where it supports survival of cells by controlling Ca-signaling from the ER to mitochondria via the IP3 receptor. Simultaneously, Sig-1R attenuates free radical damage via Nrf2 signaling. Sig-1R agonists facilitate receptor translocation from the MAM to the PM. The translocation of Sig-1R makes possible the interaction with (and regulation of) many other cytosolic or membrane-bound functional proteins, e.g. receptors, ion channels and kinases (Tables 2 and 3). Another translocation of Sig-1R from MAM to the nucleus membrane provides the possibility for interaction with chromatin-remodeling factors and thus transcriptional regulation of genes. Dysfunction of Sig-1R may have a role in disorders and thus the receptor provides novel therapeutic opportunities to treat these diseases.

Possessing both chaperone and receptor functions and the versatility of its targets the Sig-1R represents a pluripotent modulator in the living systems and is involved in the etiopathology of many diseases [14]. As a consequence, the actions of Sig-1R might be apparent only under abnormal state in the cells, e.g. at the beginning of a disease when big changes call Sig-1R to assist and maintain cell homeostasis. Sig-1R agonists function selectively only under pathological conditions thus limiting adverse side effects and have a favorable safety profile.

## 7. COMMON MECHANISMS OF NEURODEGENERATION

NDDs as diverse as AD, PD, ALS-FTLD, HD, retinal degeneration and stroke share common cellular and molecular pathological mechanisms such as excitotoxicity, calcium dysregulation and oxidative stress, mitochondrial dysfunction and ER stress. Dysfunction of glial cells may also contribute to neurodegeneration.

Fundamental cellular functions demand regulated protein folding homeostasis. Formation of misfolded proteins that may associate to toxic assemblies is the common feature of

neurodegenerative disease. ER is the subcellular organelle with the function of folding and modifying secretory and membrane proteins.

Formation of misfolded proteins and toxic aggregates point to the common pathway of NDDs: failure in normal protein folding [82]. Growing evidence suggests that (besides other cellular stress mechanisms) mainly ER-stress contributes to the development of diseased state of neurons. Chronic ER-stress and activation of unfolded protein response (UPR) may result in impaired  $Ca^{2+}$ - and redox-homeostasis and oxidative stress disturbing vital mitochondrial functions. Intracellular  $Ca^{2+}$ , released from ER, increases mitochondrial ROS production and further accumulation of ROS within ER and mitochondria, disturbing their vital functions. Chronic ER stress may also induce inflammatory processes through the UPR pathways. These events: ER-stress, oxidative stress triggered by ROS-production as well as mitochondrial dysfunction and inflammation together form a molecular web that is associated with a wide range of diseases including NDDs [83].

### 7.1. ER-stress and Unfolded Protein Response

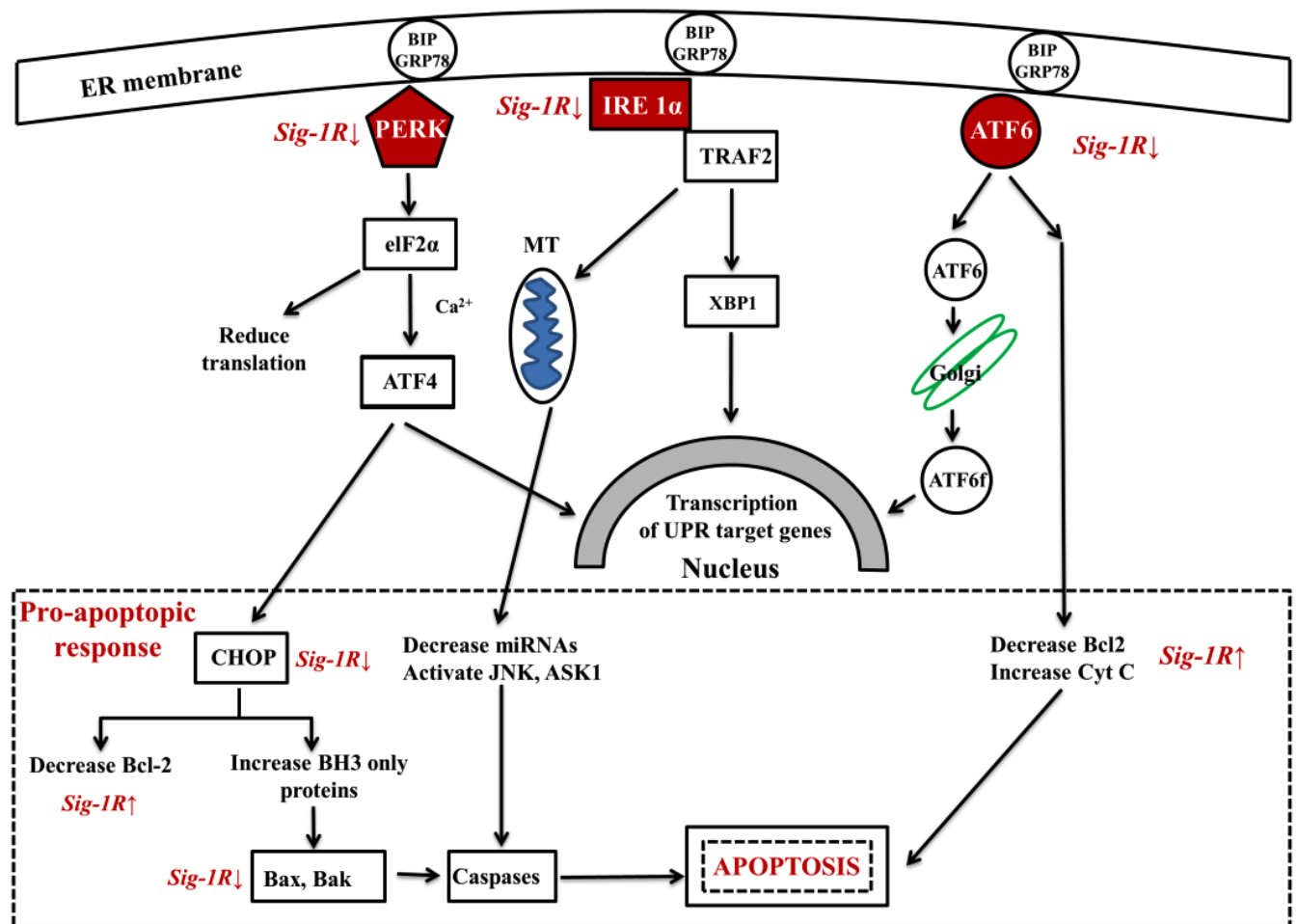
ER function can be altered in different ways and ER stress can be caused by a defective (mutated) mitochondrion, hypoxia, hyperglycemia, hyperlipidemia, viral infections, disturbances in cellular  $Ca^{2+}$  levels, redox regulation, or by oxidative stress. These so-called stress signals exhaust the ER machinery and result in buildup of unfolded proteins. An adaptive process called UPR is triggered with an aim to restore ER homeostasis. Originally, UPR has a cell protective effect: it prevents overload of the ER lumen with newly synthesized proteins and activates degradation of misfolded proteins. However, if the stress signal is severe and/or prolonged, misfolded proteins enter the mitochondria and cause dysfunction in energy production [82, 84]. As a result, cell death pathways are triggered in the form of apoptotic and pro-inflammatory reactions [85], as it will be detailed below.

Fig. 1. shows that three major pathways mediate the UPR: protein kinase RNA-like kinase (PERK), inositol requiring enzyme 1 (IRE1a) and activating transcription factor 6 (ATF6). Sustained activation of PERK triggers a signalization cascade leading to C/EBP homologous protein (CHOP) upregulation, this process inhibits the expression of anti-apoptotic B-cell lymphoma 2 (Bcl-2) and upregulates the pro-apoptotic BH3-only proteins. These events result in triggering Bak- (Bcl-2 homologous antagonist killer) and Bax (Bcl-2 like protein 4)-dependent apoptosis [86].

IRE1a may induce another signalization cascade leading to activation of c-JUN amino terminal kinase (JNK) and apoptosis signal regulating kinase (ASK), both of them trigger caspase activation and apoptotic cell death.

ATF6 activation can also decrease Bcl-2 level and increase cytochrom-C release, contributing to the activation of the apoptotic cascade [87].

In summary, UPR is a bifunctional cellular response to protein misfolding, possessing both pro- and anti-survival effects. Basal activity of the UPR is beneficial by activating the ER-assisted degradation (ERAD) machinery for clearing



**Fig. (1).** Sig-1R regulation of the three signal pathways of ER-stress activated UPR. ER chaperone BiP/GRP78 under normal conditions binds all the three ER-stress sensors (PERK: protein kinase RNA like ER-kinase; IRE1 $\alpha$ : inositol requiring enzyme 1 $\alpha$ ; ATF6: activating transcription factor 6). Under ER-stress BiP dissociates from sensors. PERK and IRE1 $\alpha$  will be phosphorylated and oligomerized, ATF6 translocates to the Golgi. (Abbreviations: eIF2 $\alpha$ : eukaryotic translation initiation factor 2 $\alpha$ ; XBP1: X-box binding protein 1 (spliced form); TRAF2: TNF-associated factor-2; ATF4: transcriptional activator factor-4; MT: mitochondrion; CHOP: c/EBF homologous protein; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2 like protein 2; Bak: Bcl-2 homologous antagonist killer; JNK: c-Jun terminal amino kinase; ASK1: apoptosis signal regulating kinase). Sig-1R activation increases cell survival by decreasing the activation of PERK, ATF6 and IRE1 $\alpha$  as well as lowering pro-apoptotic response (CHOP, Bax, Bak) and increases anti-apoptotic Bcl-2 activity.

misfolded proteins by the ubiquitin-proteasoma system and autophagy. However, sustained ER stress and chronic UPR could trigger rather a cell death than cell maintenance program [88]. Chronic ER-stress response might be linked to NDDs such as AD, PD and HD [86, 89].

Malfunction of the “ER stress – UPR – mitochondrial function - ROS production” web is central to a large diversity of illnesses. Growing evidences suggest ER stress with UPR as being a cardinal component in the development of many pathological conditions [90, 91]. Chronic UPR is thought to play a key role in neurodegenerative diseases and in many illnesses of civilization such as, diabetes, cancer, atherosclerosis, autoimmune, and cardiovascular disorders [83]. All of these disorders may have common pathological components: deficits in ER-proteostasis which lead to misfolded proteins accumulation characteristic of NDDs [86, 92]. Targeting Sig-1R by agonists may regulate ER stress

and UPR, manage ER perturbations, regulate the formation of toxic misfolded proteins, and prevent the cell-killing apoptotic pathways (Fig. 1) [93]. Similar effects are expected from the endogenous Sig-1R ligands.

## 7.2. Mitochondrial Dysfunction and Ca<sup>2+</sup>-overload of Cells

Mitochondria play critical roles in neuronal maintenance by generating ATP and biosynthetic substrates, regulating Ca<sup>2+</sup>-homeostasis and initiating apoptosis. Mitochondrial dysfunction is associated with NDDs [94, 95]. According to the most recent models, ATP insufficiency and Ca<sup>2+</sup>-dysregulation are the initial triggers of the excitotoxic cascade.

Mitochondrial fission and fusion are parts of normal organellar maintenance and particularly significant in axons. ER was identified as a crucial component of the fission ma-



chinery [96]. Fragmented mitochondria and increased fission activity are associated with NDDs such as AD, PD and HD [95]. The common membrane site MAM is very important in lipid synthesis and trafficking,  $\text{Ca}^{2+}$ -homeostasis and regulation of mitochondria-triggered apoptosis. Mitochondria-MAM dysregulation was proposed as one of the underlying causes of AD, contributing to neuronal loss [97, 98].

Sustained activation of NMDA receptors increases intracellular  $\text{Ca}^{2+}$  level, followed by failure in  $\text{Ca}^{2+}$ -homeostasis. Activation of mitochondrial permeability transition pore opening is triggered by  $\text{Ca}^{2+}$ -uptake into the mitochondrial matrix [99]. Continuous release of glutamate causes persistent activation of the NMDA receptors, leading to neuronal excitotoxicity. Excess of intracellular  $\text{Ca}^{2+}$  may contribute to neurodegeneration in many NDDs such as AD, PD and ALS [100-102].

### 7.3. Oxidative Stress

ROS are generated under different conditions, *e.g.* mitochondrial dysfunction and production by glial cells. Neurons are particularly vulnerable to glial stress [103]. Oxidative damage can affect proteins, nucleic acids and lipids. Detection of increased ROS production and oxidative damage in NDDs such as AD and PD is the best evidence for the causative effect of ROS [94, 103]. Oxidative stress also decreases the production of ATP and the antioxidant capacity (*e.g.* the level of reduced coenzymes) by impairing mitochondrial function [94].

### 7.4. Neuroinflammation, Reactive Gliosis

Reactive astrogliosis, the activation of astrocytes leads to increased expression of certain genes, *e.g.* glial fibrillary acidic protein (GFAP). Upregulation of GFAP causes astrocyte proliferation, then astrocyte migration and production of cytokines, chemokines and neurotrophic factors that aggravate brain damage.

Microglial cells are macrophage-derived resident immune cells of the CNS. As a result of dyshomeostasis in CNS, microglia is activated similarly to macrophages in the periphery showing pro-inflammatory (M1) and anti-inflammatory (M2) responses. Pro-inflammatory microglial response can cause damage to the CNS, through the release of ROS and pro-inflammatory cytokines [104]. Limiting of the inflammatory M1 and enhancing of reparative M2 responses are desired for neuroprotection.

## 8. NEUROPROTECTIVE ACTIONS BY SIG-1R LIGANDS

### 8.1. Modulation of the ER and Mitochondrial Function

Sig-1R as a chaperone modulates UPR (Fig. 1). Under normal conditions Sig-1R is in dormant state in MAM forming a complex with another ER-chaperone BiP [25]. After ER stress or ligand stimulation Sig-1R dissociates from BiP and modulates the activities of the 3 major branches of UPR (PERK, IRE1a, ATF6). ER stress is also associated with the upregulation of Sig-1R expression.

Sig-1R overexpression increases cell survival by decreasing the activation of PERK and ATF6, probably with direct protein-protein interaction. Low activity of Sig-1R destabilizes the conformation of IRE1a and decreases cell survival [105].

Sig-1R ligands ameliorate mitochondrial function, *e.g.* the agonist BHDP protected rat liver cells. Another agonist, SA4503 protected cardiomyocytes from ischemic stress. Sig-1R agonists preserved mitochondrial respiration and ATP synthesis [106, 107]. Under ER-stress Sig-1R dissociates from the BiP complex, then interacts directly with  $\text{IP}_3\text{R}_3$  and stabilizes its structure.  $\text{IP}_3\text{R}_3$  in turn promote  $\text{Ca}^{2+}$ -uptake and cell survival [23].

Sig-1R may also regulate the pro- and anti-apoptotic signals that target mitochondria: the receptor activation increases Bcl-2 expression, the elevated level of Bcl-2 interacts with  $\text{IP}_3\text{R}$  thus increasing  $\text{IP}_3\text{R}$ -mediated mitochondrial  $\text{Ca}^{2+}$ -uptake and ATP production [108, 109].

### 8.2. Attenuation of ROS Production

Increased oxidative damage was demonstrated in the tissues of Sig-1 knockout or knockdown mice [70]. Activation of Sig-1R decreases ROS-accumulation probably *via* the modulation of ROS-neutralizing proteins, upregulation of antioxidant response elements (NAD(P):quinine oxidoreductase 1 (NQO1), superoxide dismutase (SOD)).

### 8.3. $\text{Ca}^{2+}$ -homeostasis and Glutamate Activity

Activation of Sig-1Rs may dampen the excitotoxic effect of glutamate (Glu). Excessive Glu effects can be pronounced during acute events such as ischemic stroke and trauma, or milder but prolonged in chronic NDDs such as AD, PD, HD and ALS [110].

The regulation of intracellular  $\text{Ca}^{2+}$  homeostasis is one of the major mechanisms by which Sig-1R ligands perform neuroprotection. (+)-Pentazocine modulates the sustained  $\text{Ca}^{2+}$ -flux at toxic concentration of glutamate in primary rat cortical neurons [111]. Sig-1R agonists attenuate intracellular  $\text{Ca}^{2+}$  elevation in the Na-azide--glucose deprivation ischemia model [112]. Sig-1R interacts in cell survival by normalization of ER- $\text{Ca}^{2+}$  concentrations by promoting  $\text{Ca}^{2+}$ -entry into mitochondria through stabilization of  $\text{IP}_3\text{R}_3$  receptors [23]. Activation of Sig-1Rs under certain conditions inhibits NMDA receptors, which are the principal mediators of excitotoxic damage [101, 113].

### 8.4. Modulation of Glial Activity

Sig-1R ligands may ameliorate reactive astrogliosis in rodent models of stroke and ALS [114, 115]. Similarly, Sig-1R ligands modulate microglial activity in animal models of PD and ALS, affecting both M1 and M2 type microglial responses [102, 115, 116]. Sig-1R elicits neuroprotective and neurorestorative effects by balancing the inflammatory and reparative microglial responses: treating an ALS model animal with PRE-084 increased the number of glial cells associated with neuronal repair [115].

## 9. THERAPEUTIC APPLICATION OF SIG-1R MODULATION

A short list of preclinical studies and clinical trials of the cytoprotective effect of Sig-1R agonists are summarized in (Table 4).

### 9.1. Alzheimer's Disease

AD is a very complex, multifactorial disease of heterogeneous genetic and environmental background, characterized

by severe cognitive impairment and memory loss [117]. The pharmacology of Sig-1R and its role in AD was widely reviewed in 2009 [11] and in 2015 [13]. Functional deficiency of Sig-1R plays an important role in the  $\beta$ -amyloid ( $A\beta$ ) induced neuronal loss. Certain genetic combinations of Sig-1R and apolipoprotein E (apo-E) genotypes synergistically increase the risk of AD [118]. Sig-1R genotype is a determining risk factor in sporadic AD [73].

Sig-1R levels do not change considerably during normal ageing [62], however, in brains and postmortem tissues of

**Table 4. A short list of preclinical and clinical trials with cytoprotective Sig-1R agonists.**

Disease/Drug Candidate	Drug Activities	Preclinical Studies	Refs.	Clinical Trials (Phase 1,2,3)	Refs.	
<b>AD</b>	Afobazole	Sig-1R agonist, melatonin ( $MT_3$ ) agonist	Neuron culture Mice, icv $A\beta$ 25-35 (AD model)	[59, 121, 122]	-	-
	AF710B	Sig-1R agonist, M1 agonist	AD mouse model	[123]	-	-
	Anavex 2-73	Sig-1R agonist, M1 agonist	Mice, icv $A\beta$ 25-35	[124]	-	-
	Anavex 2-73	-	-	-	Phase 1 (max. dose 55mg) Phase 2a (oral, iv adm)	www.anavex.com
	Anavex 2-73+ Donepezil	ChE-ase inhibitor	Mice, icv $A\beta$ 25-35 (AD model)	[126]	-	-
	Anavex Plus (combination of Anavex 2-73 plus Donepezil)	-	Synergistic effect in AD disease models	www.anavex.com	A patent application was filed in 2016 for the combination	www.anavex.com
<b>PD</b>	PRE 084	Sig-1R agonist	PD mouse model (6-OH DOPA lesion)	[116]	-	-
<b>ALS</b>	Cutamesine (SA 4503)	Sig-1R agonist	ALS mouse model SOD1 (G93A) model +NSC34 motoneuron cells SOD1 (G93A) mouse	[139] [140] [140] [102]	-	-
	PRE-084	Sig-1R agonist	wobbler mouse	[115]	-	-
<b>HD</b>	PRE-084	Sig-1R agonist	PC63 cells	[141, 142]	-	-
	Pridopidine	Sig-1R agonist, DA stabilizer	HD mouse model	[144, 145]	-	-
<b>TBI</b> traumatic brain injury	PPBP	Sig-1R agonist	TBI neonatal mouse model	[154, 155]	-	-
<b>Retinal ganglion cell death</b>	(+) Pentazocine	Sig-1R agonist	Murine retinal cells RGC-5 cells	[157, 158]	-	-
<b>Ischemic stroke</b>	Cutamesine (SA4503)	Sig-1R agonist	-	-	Phase-2 trial	[156]

AD patients decreased level of Sig-1R was demonstrated [74, 119, 120].

Drugs activating Sig-1R are considered to be anti-amnesic and neuroprotective in NDDs such as AD. Several Sig-1R agonists (e.g. afobazole) protected cultured neurons against A $\beta$  25-35 toxicity [121, 122]. The same agonists attenuated learning and memory deficits observed in mice after intracerebroventricular injection of A $\beta$  25-35 [59].

Very recently, a mixed muscarinic-1 (M1) and Sig-1R agonist (AF710B, 1-(2,8-Dimethyl-1-thia-3,8-diazaspiro(4,5)dec-3-yl)-3-(1H-indol-3-yl)propan-1-one) has been used in AD mouse models. AF710B protects synapses *via* concomitant activation of the Sig-1R and a super-sensitive M1R, *via* a hypothetical complex of M1R-Sig-1R [123].

Anavex 2-73 (Tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride), an agonist of the intracellular Sig-1 chaperone protein is also a mixed ligand for sigma1/muscarinic receptors. It has been reported to bind to Sig-1 receptor in the high nanomolar and the muscarinic receptor in the low micromolar range. Anavex2-73 was shown to block tau-hyperphosphorylation and A $\beta$  1-42 generation in the A $\beta$  25-35 injection mouse model of AD [124] and protected mitochondria [125]. The latest studies in this mouse model demonstrated that the combination of Sig-1R agonists with donepezil showed a synergic protective effect [126], that is Sig-1R drugs offer a neuroprotective potential, also in combination with other therapeutic agents (e.g. with donepezil). Anavex Plus is a promising, potentially novel combination drug for AD, filed for patent application. It combines Anavex 2-73 Plus donepezil (Aricept), the best-selling AD drug. The combination drug produced up to 80% greater reversal of memory loss and neuroprotection compared to the administration of its individual counterparts. A patent application has been filed for Anavex Plus by the company.

According to its website (www.anavex.com), Anavex conducted a Phase 1 clinical trial in healthy men and Germany, which showed a maximum tolerated dose of 55 mg. The company completed a Phase 2a trial with Anavex 2-73 to compare oral and intravenous doses in people with mild to moderate AD at the end of 2016. Thereafter, the company plans to initiate a Phase 2/3 trial with the compound enrolling up to 300 mild to moderate AD patients.

The mechanism of Sig-1R mediated neuroprotective and anti-amnesic effects are not fully understood, but may include regulation of Ca<sup>2+</sup> [121], modulation of Bcl-2 and caspase levels [127] and attenuation of oxidative stress [128].

The protective role of Sig-1R activation in AD is yet under discussion. In heterogeneous knock-out mice the Sig-1R deficiency reduced A $\beta$  25-35 induced hippocampal neuron death and cognitive deficits [129]. Sig-1R deficiency or blockade can reduce A $\beta$  enhanced Ca<sup>2+</sup>-influx and prevent neurotoxicity [130]. The discrepancy in the scientific literature is hard to be reconciled, perhaps exact timing of Sig-1R activation might explain the contradictory effects. Although preclinical evidences suggest that Sig-1R agonists might be

useful in treating AD, no selective Sig-1R agonist is currently available for clinical use.

## 9.2. Parkinson's Disease

Likewise in Alzheimer's disease [74] Sig-1Rs are down-regulated in the brains of early stage PD patients [75, 131]. Recently, the pharmacological stimulation of the Sig-1R has shown some neurorestorative effects in experimental PD [116], the treatment of mice with the Sig-1R agonist PRE-084 caused both behavioral and histological improvements in the 6-hydroxydopamine-lesion mouse model of PD. Daily treatment of mice with 0.3 mg/kg PRE-084 during 5 weeks improved forelimb use, together with a modest recovery of dopamine levels. PRE-084 as Sig-1R agonist also upregulated the neurotrophic factors BDNF and GDNF and activated the trophic factor mediators ERK1 and ERK2 [116]. These results show that the restoration of synaptic connectivity correlates with the functional recovery in PD. As inflammation contributes to the pathophysiology of PD, the attenuation of M1 microglial response by PRE-084 treatment supports neuronal recovery in the PD mouse model. *In vitro* experiments where wild type and Sig-1R knock down CHO-cells were treated with dopamine suggest that Sig-1Rs are important endogenous substrates that counteract the dopamine cytotoxicity [132]. The results show that the Sig-1R-NF- $\kappa$ B-Bcl-2 pathway plays a crucial role against dopamine induced apoptosis.

## 9.3. Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobe Dementia (FTLD)

ALS is characterized by the progressive loss of motoneurons in the brainstem, motor cortex and spinal cord causing paralysis and death. Pathological hallmarks include calcium dysregulation and cytotoxicity, ER-stress and mitochondrial dysfunction [133], accumulation of misfolded proteins, neuro-inflammation and degradation of motoneurons [102]. It was demonstrated that a loss of Sig-1R is causative for a juvenile form of ALS (ALS16) and collapse of MAM is a common pathomechanism in both Sig-1R and SOD-1 linked ALS [134]. Mutations in the Sig-1R gene were found in patients with FTLD-ALS and a juvenile form of ALS [79, 135]. The receptor mutation lies very close to an area of chromosome 9, called the ALS-FTLD locus, which researchers have linked to ALS and FTLD [136]. A significant reduction of Sig-1R protein level was found in the lumbar spinal cord of ALS patients [137]. Aberrant modifications of Sig-1R ((abnormal accumulation in ER structures, enlarged C-terminals) were found in  $\alpha$  motoneurons during the pathogenesis of ALS [137]. Since Sig-1R can regulate ERAD [138], this Sig-1R accumulation and co-localization with aberrant protein assemblies may reflect a compensatory effort by Sig-1R to clear misfolded proteins in ALS.

Attempts to target Sig-1Rs to treat ALS gave promising results in model experiments both *in vitro* and *in vivo*. The protective role of Sig-1R in motoneurons of an ALS mouse model has been confirmed [139]. SA4503, a Sig-1R agonist suppressed motor neuron damage in model experiments, both *in vitro* (NSC34 motor neuron cells) and *in vivo* (in the SOD1 (G93A) mouse model) [140]. PRE-084 treatment prolonged life span and slowed the progression of ALS symp-

toms in a SOD1 (G93A) mouse model of ALS [102]. Chronic (8 weeks) PRE-084 treatment (0.25 mg/kg, i.p., three times a week) improved motoneuron survival and locomotor performances in the wobblers mouse, an animal model of spontaneous motoneuron degeneration [115]. Experimental results suggest that targeting Sig-1R with agonists may help ameliorate protein aggregation and slow disease progression by enhancing the chaperone activity of Sig-1R.

#### 9.4. Huntington Disease (HD)

HD is a “polyglutamine” (polyQ) disease, a genetic disorder: an autosomal dominant mutation in the huntingtin gene by a repetitive CAG region. HD is characterized by progressive motor and cognitive deficits resulted by selective neuronal loss.

Recent studies in the neuronal HD model (the cell line PC6.3) showed decreased Sig-1R levels in the presence of a mutant huntingtin protein expression (containing 120 glutamine repeats, 120 polyQ or 120Q huntingtin, [141]. Administration of PRE-084 to the mutant PC6.3 cells restored the deficits in Sig-1R protein levels caused by the mutant huntingtin expression, probably by modulation of post-transcriptional processes [141]. PRE-084 also promoted cell viability and decreased caspase-3 and caspase-12 (an ER resident caspase) cleavage, probably by attenuation of ER stress through the activation of Sig-1R. PRE-084 can perform neuroprotection also by modulation of the calpastatin/calpain system [142] which positively affects NF- $\kappa$ B signaling to upregulate various cellular antioxidants and decrease ROS levels [141].

Sig-1R is involved in degradation of intranuclear inclusions in a cellular model of HD [143].

A registered drug, pridopidine, originally described as a dopamine stabilizer, improves HD motor symptoms as measured in clinical trials. Binding studies shows that Sig-1R is a high affinity receptor for pridopidine: the compound is also a Sig-1R agonist. HD mouse model experiments demonstrate that Sig-1R mediates the beneficial effect of pridopidine by preventing spine loss of striatal medium spiny neurons in HD [144]. Activation of Sig-1R and the subsequent upregulation of BDNF pathway represents the core component of the mode of action of pridopidine (promoting neuronal plasticity and survival) [145].

#### 9.5. Traumatic Brain Injury

Traumatic brain injury (TBI) is one of the leading acute neurological disorders causing death and disability worldwide [146]. Very few effective treatments are available to mitigate neuronal damage and patients need long term care for physical and psychosocial rehabilitation. The outcome and costs of treatment after TBI are difficult to predict due to the physical disability combined the emotional and psychosocial consequences of the trauma [147]. The high rate of blast-related TBIs resulting from current combat operations profoundly affects the health and quality of life of service members and veterans during times of both war and peace.

Physical trauma to the brain initiates a series of inflammatory reactions, which includes release of intracellular

products from damaged cells, microglia activation, cytokine production, and recruiting peripheral inflammatory cells into damaged areas. Microglia function is critical in response to brain injury [148]. Upon activation, microglia undergoes morphological transformation, secretes inflammatory mediators, and clears tissue debris by phagocytosis [149]. However, activated microglia can aggravate brain injury and impair its restoration [150]. A cumulative evidence suggests that activated microglia can release pro-inflammatory cytokines (e.g., TNF- $\alpha$ ) and nitric oxide, which extend the neuronal injury after TBI [151]. Therefore, inhibition of microglial activation can protect brain tissue from the sequelae of TBI [152], and can be an important element of therapeutic approaches against TBI. Chronic microglial responses may be responsible for neurodegeneration in many neurological disorders and the role of Sig-1Rs might be to “switch-off” microglia after they responded to an injury allowing for microglial cells to leave site of damage [153].

Considering the presence of Sig-1R on microglial cells [11] and the effects Sig-1R agonists on reducing microglia activation [102], it was postulated and recently confirmed that activation of Sig-1R receptors after TBI can reduce lesion volume, lessen brain edema, and attenuate neurological deficits [154]. The Sig-1R agonist PPBP (4-phenyl-1-(4-phenylbutyl)piperidine) protects brain against newborn excitotoxic brain injury in an established neonatal mouse model by inhibiting microglial activation *in vivo* [155].

#### 9.6. Other Diseases

Sig-1R agonists have been tried in animal models of different disorders and also used for the treatment of different diseases. Thus, cutamesine (SA4503) was used for recovery enhancement after ischemic stroke [156]. (+)-Pentazocine reduced NMDA-induced retinal ganglion cell death: recently Sig-1R is a promising therapeutic target for retinal neurodegenerative disorders [157, 158].

### 10. DIMETHYLTRYPTAMINE AS A NATURAL SIG-1R LIGAND

The discovery of the tryptamine analogue DMT as a natural ligand of the Sig-1R has moved the 40-year long fuzzy history of both of these molecules toward clarification. DMT was classified as an endogenous hallucinogen [159, 160] with exact physiological function unclear [161]. Ayahuasca, a psychoactive Amazonian ethnomedicinal brew, raised increased scientific and public interest during the last two decades. Ayahuasca is prepared from two admixture plants (Banisteriopsis caapi and Psychotria viridis) the latter provides the psychoactive alkaloid DMT [162, 163]. More than 40 years of research has proven to be insufficient to provide a proper neurobiological description for the role of DMT as endogenous hallucinogen. This was in part due to a paradigm problem in which DMT has been primarily studied in terms of being “hallucinogen” since it has been known to produce false perceptions. These effects presumably reflect action on serotonin (5-HT) receptors (5-HT<sub>1A</sub>, -2A and -2C) [164], and very probably involve the metabotropic glutamate receptors [165]. However, the Sig-1R action of DMT may turn out to be more revealing and more relevant for its physiological function. The main ingredients of the ayahuasca

sca are DMT and the  $\beta$ -carboline derivative alkaloid harmine [166]. It is reasonable to suppose that DMT from this exogenous source can exert Sig-1R agonist effect and mitigate a wide variety of problems related to the disorganized web of mitochondrial dysfunction, ER stress, and UPR.

DMT is considered as a natural ligand of the Sig-1R [3]. It is assumed that the Sig-1R might be involved in the DMT-induced psychedelic effects [167]; however, this is probably not so, since many drugs—typically non-hallucinogens—bind to the Sig-1R with higher affinity than DMT. Another vista has been opening up instead. If the Sig-1R mitigates ER stress [71], promotes neuronal survival against oxidative stress [70], and regulates immune processes [168], one may attribute the same role to DMT [169]. Since the Sig-1R is also known to regulate morphogenesis of neuronal cells, such as neurite outgrowth, synaptogenesis, and myelination [170]; neurorestorative effects are reasonably expected from DMT. In a recent paper [169] Frecska *et al.* concluded that the function of DMT may extend central nervous activity and involve a more universal role in cellular protective mechanisms. These authors provided converging evidence that the role of DMT can be conceptualized along the line of adaptive mechanisms like neuroprotection, and immunity. The theoretical work was followed by experimental studies and Sig-1R mediated anti-inflammatory [80] and anti-hypoxia effects [171] of DMT were verified *in vitro*.

## CONCLUSION

Sig-1R is an intracellular receptor acting as ER-chaperone (residing in the MAM) with unique pharmacological profile. It has also a unique amino acid sequence and steric structure among the receptor proteins. DMT is the endogenous ligand of Sig-1R. Oligomerization and translocation from the MAM to different biological membranes are key functional properties. The receptor has versatile cellular function and binds ligands of very diverse structure. Sig-1R is a ligand-regulated molecular chaperone which is not coupled to G-proteins. The main physiological functions (modulation of  $Ca^{2+}$  signaling, inhibition of voltage-dependent  $K^+$  channels, release of various neurotransmitters, immunomodulation) are known, however, the signal transduction pathways are not yet clarified.

Sig-1R is a pluripotent modulator of cellular events, regulating the inter-organelle communication and cell survival by increasing stress-response signaling. The receptor can interact with many proteins (with diverse structure and function) and can form oligomeric assemblies and heterodimers with other proteins. The existence of different oligomeric forms might provide a wide adaptability, which enables Sig-1R to interact with structurally different substrates.

Many marketed psychotropic drugs (fluvoxamine, donepezil) have affinity on Sig-1R, however, the mechanism of action is not yet clear. Receptor binding affinity and pharmacological activities frequently do not show good correlation, the molecular basis of ligand efficacy is to be discovered. Although Sig-1R agonists show neuroprotective effect in cellular and animal models, no effective registered neuroprotective drugs are on the market. Sig-1R agonists would be

ideal drug candidates for translational medicine, because the known ligands have limited side effects: their modulatory action starts only under pathological conditions. A further work is required for clarifying the cellular mechanisms and molecular targets of Sig-1R. Application of Sig-1R agonists alone, very probably, will not be sufficient for the treatment of neurodegenerative diseases.

## LIST OF ABBREVIATIONS

AChE	=	Acetylcholine esterase
AD	=	Alzheimer's disease
ALS	=	Amyotrophic lateral sclerosis
ASK	=	Apoptosis signal-regulating kinase
ATF6	=	Activating transcription factor 6
ATP	=	Adenosine triphosphate
BACE	=	Beta-site APP cleaving enzyme
Bak	=	Bcl-2 homologous antagonist killer
Bax	=	Bcl-2 like protein 4
Bcl-2	=	B-cell lymphoma 2
BiP	=	Binding immunoglobulin protein
BDNF	=	Brain derived neurotrophic factor
CNS	=	Central nervous system
DMT	=	Dimethyltryptamine
DTG	=	1,3-Di-o.tolyl guanidine
ER	=	Endoplasmic reticulum
ERAD	=	ER-associated degradation
ERG2	=	Yeast sterol isomerase
ERK	=	Extracellular signal regulated kinases
FTLD	=	Frontotemporal lobar degeneration
FRET	=	Forster resonance energy transfer
GDNF	=	Glial cell-derived neurotrophic factor
GFAP	=	Glial fibrillary acidic protein
GPCR	=	G-protein coupled receptors
GSK3B	=	Glycogen synthase kinase 3b
GTP	=	Guanosine triphosphate
HD	=	Huntington disease
IRE1	=	Inositol requiring enzyme 1
IP <sub>3</sub> R	=	Inositol-triphosphate receptor
ID	=	Intrinsically disordered
JNK	=	c-Jun amino terminal kinase
MAM	=	Mitochondrion associated ER-membrane
M1R	=	Muscarinic-1 receptor
NDD	=	Neurodegenerative diseases

NFκB	=	Nuclear factor-kappa B
NMDA	=	N-methyl-D-aspartate
Nrf2	=	NF-E2-related nuclear factor 2
PCP	=	Phencyclidine
PD	=	Parkinson's disease
PERK	=	Protein kinase RNA like ER-kinase
PM	=	Plasma membrane
ROS	=	Reactive oxygen species
Sig-1R	=	Sigma-1 receptor
Sig-2R	=	Sigma-2 receptor
SOD	=	Superoxide dismutase
TBI	=	Traumatic brain injury
TNFα	=	Tumor necrosis factor α
UPR	=	Unfolded protein response

### CONSENT FOR PUBLICATION

Not applicable.

### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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