Targeting ligand-operated chaperone sigma-1 receptors in the treatment of neuropsychiatric disorders

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Abstract

Introduction—Current conventional therapeutic drugs for the treatment of psychiatric or neurodegenerative disorders have certain limitations of use. Psychotherapeutic drugs such as typical and atypical antipsychotics, tricyclic antidepressants, and selective monoamine reuptake inhibitors, aim to normalize the hyper- or hypo-neurotransmission of monoaminergic systems. Despite their great contribution to the outcomes of psychiatric patients, these agents often exert severe side effects and require chronic treatments to promote amelioration of symptoms. Furthermore, drugs available for the treatment of neurodegenerative disorders are severely limited.

Areas covered—This review discusses recent evidence that has shed light on sigma-1 receptor ligands, which may serve as a new class of antidepressants or neuroprotective agents. Sigma-1 receptors are novel ligand-operated molecular chaperones regulating a variety of signal transduction, ER stress, cellular redox, cellular survival, and synaptogenesis. Selective sigma-1 receptor ligands exert rapid antidepressant-like, anxiolytic, antinociceptive and robust neuroprotective actions in preclinical studies. The review also looks at recent studies which suggest that reactive oxygen species might play a crucial role as signal integrators at the downstream of Sig-1Rs

Expert opinion—The significant advances in sigma receptor research in the last decade have begun to elucidate the intracellular signal cascades upstream and downstream of sigma-1 receptors. The novel ligand-operated properties of the sigma-1 receptor chaperone may enable a variety of interventions by which stress-related cellular systems are pharmacologically controlled.

Keywords

sigma receptor; sigma-1 receptor; molecular chaperone; depression; antidepressant; schizophrenia; neurodegenerative disorder; Parkinson's disease; Alzheimer's disease; stroke; ER stress; chaperone; endoplasmic reticulum; reactive oxygen species

1. Introduction

It is a long time since clinical research or even daily clinical practices have proven limitations in use of psychotherapeutic drugs targeting monoaminergic systems. One of the most urgent tasks in current psychopharmacology research may be thus to introduce new classes of central nervous system (CNS) drugs that interact with other systems. From the

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Declaration of interest
All authors declare no conflict of interest.

1950's to 1960's, we experienced an incomparable breakthrough in psychopharmacology where prototypes of currently used antipsychotics, antidepressants, benzodiazepines, and mood stabilizers had been discovered during only about 15 years[1]. In spite of untiring basic research of psychopharmacology pursued in following 50 years, changes seen at bedsides are not much dramatic in some instances. Thus, large endeavors continue to improve monoaminergic drugs (e.g., seeking drugs with higher selectivity, dual activities on different monoamine receptors, or activity on autoreceptors) or to discover new molecular targets[1].

The progress of psychopharmacology has been tightly linked to the progress of basic neuroscience. The establishment of the monoamine theory was apparently aided by the discovery of neurotransmitters and the emerged concept of brain receptors. Looking back into the last two decades, the discrepancy between the progress of basic neuroscience/ neuropharmacology and that of clinical psychopharmacology appears to be more obvious. Nevertheless, if we can assume that the progress of these disciplines essentially synchronizes in the long viewpoint, the new concepts established in the 1990s of neuroscience research, namely synaptogenesis and neurogenesis, should be important discoveries to look over the scope of the future drug development. Synthetic compounds that enable pharmacological manipulations of these brain phenomena may be potential candidates of the next generation of CNS drugs. A number of recent studies indeed implicate synaptogenesis/neurogenesis in the pathogenesis or pathophysiology of several neurological and psychiatric disorders[2].

The sigma receptor ligands have been expected to serve as the next generation of psychotherapeutic drugs[3–7]. The early misconception falling the sigma receptor into a subtype of opioid receptors and its mysterious molecular entity, however, impeded the introduction of the specific ligands to clinical trials. Nevertheless, the understanding of the molecular function of sigma receptors has been dramatically improved in the last 10 years[3,5,6]. The sigma receptor is now confirmed to be a non-opioid, endoplasmic reticulum (ER) protein[3,5,6]. The sigma receptor consists of at least two subtypes, sigma-1 and −2, and regulates a variety of cellular functions, such as Ca^{2+} signaling, ion channel firing, protein kinase translocation/activation, cellular redox, neurotransmitter release, inflammation, cellular differentiation, neuronal survival, and synaptogenesis[3,5,6,8,9]. Recent studies demonstrated that the sigma receptor is also involved in pain, immune reactions, liver protection, and cancer proliferation[8,10–14]. Since several recent reviews comprehensively discuss overall functions and properties of sigma receptors[3,4,6,11,12], this review mainly focuses on the most recent findings exploring signal transductions of the type-1 sigma receptor, particularly those crucial for regulation of neuronal survival, synaptogenesis, and neurogenesis. By doing so, this review article tempts to elucidate specific and relevant clinical targets of sigma-1 receptor (Sig-1R) ligands.

2. Sigma-1 receptor: the ligand-operated molecular chaperone

2-1. Molecular function of the Sig-1R

The Sig-1R is an integral membrane protein with a 24-kDa molecular mass. Sig-1Rs are expressed predominantly at ER membranes, and regulate a variety of cellular functions in neuronal, glial and peripheral cells[10,15–19]. Two hydrophobic domains residing at the N-terminus (a.a. 11–29) and the center of the Sig-1R (a.a. 92–112) comprise membrane-spanning α-helices[20–22]. A recent study discovered that the C-terminus (a.a. 113–223) contains molecular chaperone activity[20]. Purified C-terminal polypeptides (a.a. 116–223) can completely inhibit heatshock-induced aggregation of citrate synthases in the *in vitro* light scattering assay[20]. The precise amino acid sequence necessary for the chaperone activity is however not yet defined. The C-terminus is resistant against the chymotrypsin

digestion in microsomal preparations. Antibodies specific to the C-terminus fail to access the antigenic sites without detergent-permeabilization of ER membranes[20]. These findings indicate the ER-lumenal localization of the C-terminus.

The Sig-1R shares no homology with any mammalian proteins including all types of molecular chaperones[11,23]. The major function of molecular chaperones at the ER is to promote the proper folding of newly synthesized proteins. ER chaperones also regulate the proteasomal protein degradation by transferring misfolded proteins to the ER-associated degradation (ERAD) machinery[24]. These actions of molecular chaperones are crucial for cells to prevent accumulation of toxic protein aggregates, thus promoting cellular survival under cellular stress[24]. Like other molecular chaperones, Sig-1Rs or its upregulation are shown to suppress cell death incurred by various cellular stress in primary cortical neurons, retinal ganglion cells, hamster ovary cells, neuroblastoma and glioma[20,25–28]. A recent genetic study, however, found that a nonpolymorphic mutation (c. 672*51G>T) in the 3'-untranslated region (UTR) of the Sig-1R gene, which promotes the upregulation of Sig-1Rs, is strongly associated with frontotemporal lobar degeneration with motor neuron disease (FTLD-MND) in an Australian pedigree[29]. The altered Sig-1R expression in the brain appears to cause depositions of ubiquitinated inclusion bodies composed of heterogeneous nuclear ribonucleoproteins, such as TDP-43 and FUS[29]. This finding indicates that the "constitutive" increase of Sig-1Rs in cortical, hippocampal and motor neurons might cause an imbalance in a system transporting nuclear ribonucleoproteins from the cytoplasm to the nucleus. The expression level of Sig-1Rs seems to be tightly regulated in a context-dependent manner (e.g., ER stress-induced upregulation), and its upregulation may not be merely always beneficial for cellular survival.

The mechanism regulating chaperone activity of the Sig-1R involves the physical protein-protein interaction between Sig-1Rs and another ER chaperone BiP/GRP78 (Fig. 1)[20,23]. When the Sig-1R forms a complex with BiP, the chaperone activity is minimized. In contrast, the Sig-1R dissociated from BiP exerts the maximum chaperone activity. Importantly, several synthetic compounds possessing the agonist property of the Sig-1R promote the dissociation of the Sig-1R from BiP, thus Sig-1R agonists gain the chaperone activity of the Sig-1R[11,20]. Conversely, Sig-1R antagonists reinforce the association of the two proteins, thus minimizing the chaperone activity of the Sig-1R[11,20]. Importantly, Ca^{2+} ion in the ER lumen also reinforces the association at its physiological concentrations (~0.5 mM)[20]. This Ca^{2+}-dependent regulation of the Sig-1R–BiP association is therefore placed under a control by G protein-coupled metabotrophic receptors (GPCRs). IP_3 receptors activated by the stimulation of GPCRs lead to the depletion of ER Ca^{2+}, which in turn triggers the dissociation of Sig-1Rs from BiP[20]. A recent study demonstrated that oxidative stress caused by the treatment with the xanthine:xanthine oxidase increases the association of BiP with Sig-1Rs as well as phosphorylation of Sig-1Rs in primary ganglion cells[25]. The Sig-1R agonist (+)pentazocine was shown to promote the dissociation of BiP from Sig-1Rs, which concomitantly inhibits the phosphorylation of Sig-1Rs and apoptosis[25].

The Sig-1R is the first molecular chaperone whose chaperone activity is found to be regulated by synthetic compounds in a clear agonist-antagonist manner[23]. The unique characteristic may provide a novel pharmacological opportunity to alleviate accumulation of misfolded proteins. Table 1 summarizes Sig-1R ligands that are most recently examined in preclinical studies. Chemical engineering of selective, high-affinity Sig-1R ligands is currently one of the most active areas. Novel Sig-1R ligands and imaging tracers synthesized in the last 5 years are also summarized in Table 1.

2-2. The unique subcellular localization of Sig-1Rs

Recent studies demonstrated that Sig-1Rs are highly clustered at specialized ER domains that are physically associating with mitochondrial outer-membranes (i.e., the mitochondria-associated ER membrane: MAM)[20]. The discrete subcellular distribution of Sig-1Rs may restrict the number/kinds of ER proteins stabilized by Sig-1R chaperones, but also implicates the potential involvement of Sig-1Rs in mitochondrial functions[23]. Sig-1Rs are shown to chaperone IP_3 receptors localized to MAMs[20]. Ca^{2+} influxed through IP_3 receptors to mitochondria is known to activate the ATP synthesis via activation of the TCA cycle, whereas overloading of mitochondrial Ca^{2+} causes apoptosis, especially when cells are under a chronic stress[30]. Thus, Sig-1Rs chaperoning IP_3 receptors at the MAM could regulate mitochondrial bioenergetics and cell death.

The chronic administration of Sig-1R ligands or cellular stress is shown to promote redistribution of Sig-1Rs from MAMs to peripherals of ER membranes or to nuclear envelopes[20]. This relocation may possibly increase the number or kinds of client proteins stabilized by Sig-1R chaperones. A line of studies showed that Sig-1Rs physically associate with ion channels at the plasma membrane[22,31,32], which results in tonic inhibition of the channel activity. If the mechanism of Sig-1Rs regulating ion channels involves chaperoning of ion channels by Sig-1Rs, the C-terminal chaperone domain of the Sig-1R should be relocated from the ER lumen to the cytoplasmic face of the ER membrane, or Sig-1Rs need to translocate to plasma membranes for the lateral interaction with plasma membrane proteins. In certain types of cells Sig-1Rs are sitting at ER subdomains that are close enough for the association with proteins at plasma membranes[33] (but, this process may still require a flip-flop movement of the chaperone domain from the ER lumen to the cytoplasmic face of the ER membrane). An electron microscopic study found that Sig-1Rs are clustered at the ER subdomains close to post-synaptic membranes of cholinergic motor neurons in the brainstem and spinal cord[33]. A recent study suggested that ER-specific lipids microdomains composed of cholesterol and ceramides contribute to clustering and distribution of Sig-1Rs at ER membranes[34]. The other possible mechanism in Sig-1Rs' chaperoning plasma membrane proteins may involve the receptor translocation. After translocating from ER to plasma membranes, Sig-1Rs might compose protein complexes with ion channels via the lateral protein-protein association at plasma membranes. In this case, one possibility is that the association between Sig-1Rs and ion channels might be achieved at the ER before the complex enters the ER-Golgi secretory pathway. A recent study demonstrated that the N-terminus di-arginine motif xRRx regulates protein localization via the retrograde Golgi-to-ER membrane traffic pathway involving COP-I vesicles[35]. The motif is conserved in over 150 of mammalian membrane proteins that include the Sig-1R, plasma membrane ATP-sensitive potassium channel (Kir6.1/2), and $GABA_B$ receptor GB_1 subunit[35]. Thus, protein-protein interactions that mask the di-arginine motif and thus hinder the motif from the recognition by the Golgi-to-ER retrieval machinery might be able to trigger the departure of proteins from the ER to plasma membranes.

2-3. Signaling cascades regulated by Sig-1Rs

Recent studies begin to unveil the outline of signaling cascades upstream or downstream of Sig-1Rs. Signaling pathways reported in the last 5 years are summarized in Fig. 2. Several studies demonstrated that Sig-1Rs regulate translocation/activation of both protein kinase A and C, which play important roles in gene regulation (e.g., *BDNF* gene) and neuronal plasticity in the CNS[36–38]. Sig-1Rs can modulate activity of some other kinases downstream of trophic factor or monoamine receptors (e.g., MAP kinases, PI3 kinase) [8,39,40]. A recent study demonstrated that Sig-1R agonists, such as dehydroepiandrosterone (DHEA) and PRE084, promote survival of newborn neurons in the

dentate gyrus by activating the Akt-mTOR-p70S6k pathway[41]. It is noteworthy that mTOR-p70S6k–dependent synapse formation is recently discovered as a key element of the rapid antidepressant-like action of drugs[42], and that one of the most unique actions of Sig-1R agonists are their rapid antidepressant-like effect as proven by several studies[11].

Similar to other molecular chaperones, Sig-1Rs are rapidly upregulated under cellular stress. For example, the protein level of Sig-1Rs becomes two folds just 1 hr after glucose deprivation in Chinese hamster ovary cells[20]. This property of rapid upregulation should affect the gross activity of Sig-1R chaperones in the cell. At the *vivo* level, the region-specific upregulation may contribute to specifying organs or their substructures where Sig-1R ligands are supposedly the most active. Sig-1Rs ubiquitously express in the brain with a certain discrete distribution pattern (e.g., the enrichment in nuclei of midbrain and brainstem)[15]. However, their brain distribution is altered under pathological conditions. For example, the self-administration of methamphetamine is shown to promote upregulation of Sig-1Rs in the olfactory bulb, substantia nigra, and ventral tegmental area[43]. Sig-1R ligands including antidepressants also promote the upregulation of Sig-1Rs in both nervous and peripheral systems. For example, fluvoxamine promotes the Sig-1R expression in the left ventricle of the hypertrophic heart, therefore prevents the heart failure[44]. Detailed transcriptional regulations of the Sig-1R gene expression are not systematically examined until now. However, the immediate-early gene fos-related antigen 2 (fra-2) is the transcriptional factor that was recently discovered as an upregulator of Sig-1Rs in cocaine-sensitized mouse brains[45].

The feature of molecular chaperones being able to interact with a variety of proteins might in part explain the wide range of cellular actions involving Sig-1Rs (Fig. 2). It is estimated that one type of molecular chaperones could contribute to stabilization of over a hundred of proteins[46]. The association between a molecular chaperone and the client misfolded protein is thus not highly selective[47]. It is unknown at present how many proteins Sig-1R chaperones stabilize. Recent studies, however, suggest that reactive oxygen species (ROS) might play a crucial role as signal integrators at the downstream of Sig-1Rs[48,49]. Sig-1Rs appear to be intrinsically suppressing the accumulation/formation of ROS in the cell since the knockdown of Sig-1Rs *per se* (i.e., without any additional cellular stress) can promote the accumulation of ROS[49]. The source of ROS generated by the Sig-1R knockdown is not identified, but possibly involves both mitochondria and ER. Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a ROS-responsive transcription factor that binds to the antioxidant response elements (ARE) within the promoter of antioxidant enzymes[50]. Nrf2 is phosphorylated in response to the PKC, PI3K and MAPKs[50]; all those molecules are modulated by Sig-1Rs (Fig. 2). Whether Sig-1Rs regulate the crosstalk between these kinases and Nrf2 is an interesting open question.

Various signaling pathways are modulated by Sig-1Rs in a cell type- and condition-dependent manner (Fig. 2). However, it is important to stress that, in many cases, Sig-1R agonists or upregulation of Sig-1R proteins leads to suppression of oxidative stress[25,40,44,49]. Thus the diverse range of Sig-1R–related signaling cascades seems to be integrated toward the promotion of cellular survival/protection. Further, in most cases, agonists *per se* do not exert effects under normal conditions, but they modulate activity of signaling pathways when they are once activated or perturbed by their stimulants or cytotoxic insults[5]. The unique "modulatory" effect of Sig-1R ligands might be explained partly by the property of molecular chaperones[5,12], which exert their action mostly under cellular stress that triggers misfolding of proteins. Though the mechanism of the "modulatory" action needs further studies to be fully clarified, Sig-1R ligands seem to possess an ideal property as a therapeutic drug where the drug is effective/active only under pathological conditions, but inactive/safe under the normal healthy condition.

3. Roles of Sig-1R in synaptogenesis and neuronal plasticity

3-1. Dendritic spine

Dendritic spines are small cytoplasmic projections surrounded by plasma membranes protruding from dendrites of neurons. In the mature brain approximately 90% of the excitatory synapses are located at dendritic spines[51]. Young dendritic spines are long and have filopodia, the slender microspikes at the plasma membrane, while matured spines shorten their length and have fewer filopodia[51]. Dendritic spines have been found to exhibit motility on a seconds-to-minutes timescale both in cultures and *in vivo*. The actin-based motility of dendritic spines is controlled by synaptic activity. AMPA- or NMDA-receptor activation inhibits the actin dynamics of the dendritic spines, while long-term potentiation (LTP) causes an increase in the size of spine heads in the immature hippocampus[51]. LTP has also been associated with an increase in recycled endosomes, polyribosomes, and mitochondria in the dendritic spines[51]. In general, decreased efficiency in neuronal communication, due in part to changes in the dendritic spine density and morphology, is likely a cause of certain symptoms observed in mental retardation, schizophrenia, Parkinson's disease, autism, Alzheimer's disease, obsessive-compulsive disorder, and addiction[52]. Recent emerging evidence demonstrates that Sig-1Rs regulate activity of NMDA receptors, LTP, membrane protrusion and neuronal differentiation[3,5]. Further, Sig-1R ligands have been shown to ameliorate behaviors related to some of above-mentioned human diseases[3]. These findings suggest that Sig-1Rs may play important roles in regulation of synaptic functions, possibly those involving synaptogenesis.

Dynamic actin filaments regulate the spine morphology, thus playing a crucial role in formation of synaptic plasticity. The small GTPase family, including Rac1, cdc42 and RhoA, are key molecules regulating actin organization. Cdc42 is required for initiating the formation of filopodia/neurite, while RhoA regulates spine retraction[53]. The Rac GTPase together with its specific guanine nucleotide-exchange factor (GEF) contributes to forming and maintaining dendritic spines in neurons[53]. The polarity protein PAR-3 locates Rac1 GEF Tiam1 specifically at the tip of filopodia, and regulates Rac1 activation therein to promote formation of spine heads[54]. Mislocalization of Tiam1 due to aberrant activity of PAR-3 causes unregulated Rac1 activation, resulting in the reduction in normal dendritic spine formation[54]. The Rac1-GEF Tiam1 complex also couples to NMDA receptors, and regulates the NMDA receptor-dependent spine formation and dendritic aborization[55]. The conversion of Rac-GDP to Rac-GTP is dependent on the activity of Ca^{2+}/calmodulin (CaM)-dependent protein kinases (CaMKs), which reside at lipid raft microdomains at synapses. Lipid raft-associated CaMKs are thus important factors linking Ca^{2+} signals to actin remodeling[56]. Although Sig-1Rs was shown to associate with the cytoskeletal adaptor protein ankyrin-B[5], whether Sig-1Rs regulate cytoskeleton polymerization involved in synaptogenesis had not been tested until a recent finding demonstrated that Sig-1Rs regulate synaptogenesis via the Tiam1-Rac pathway[48]. This finding is discussed in the section 3-2.

3-2. Sig-1Rs control synaptogenesis and neuronal morphogenesis

Tsai and colleagues (2009) recently discovered that Sig-1Rs promote dendritic outgrowth and dendritic spine maturation by regulating the Tiam1-Rac1-induced actin polymerization[46]. Hippocampal primary neurons lacking Sig-1Rs exhibit aberrant dendrite morphogenesis that is characteristic to decreased matured dendritic spines together with numerous long, thin filopodia lacking the head structures on the tip (Fig. 3). The reduction of dendrite branching and the spine density also resulted in the significant decrease of functional synapses[46].

The underlying mechanism of Sig-1R's regulation of synaptogenesis appears to involve the regulation of ROS production/scavenging. The loss of Sig-1Rs leads to the ROS accumulation, activation of caspase-3 and ROS-induced degradation of the Rac-GTP activator Tiam1[46]. The most recent microarray analysis using rat primary neurons infected with Sig-1R siRNAs also demonstrated that the Sig-1R knockdown leads to alterations of a cluster of transcripts implicated in remodeling of the actin-based cytoskeleton network[57]. The transcripts involve Rac1, RhoA, IP3K–A, Rho/Rac GEF2 and Ca^{2+}/calmodulin-dependent protein kinase I gamma. It is also noticeable that the ARP2/3 transcript, which is involved in actin polymerization, is significantly decreased in Sig-1R–depleted neurons. Thus, Sig-1R may regulate dendritic spine formation by controlling stability and expression of the actin-based cytoskeletons. Because Sig-1Rs are also important in lipid biosynthesis and in lipid raft formation[32], it is also reasonable to speculate that Sig-1Rs may affect the recruitment and clustering of these proteins at lipid rafts of plasma membranes.

3-3. Diseases related to abrupt synaptogenesis and plasticity

Alterations in the density, shape, and size of dendritic spines have been linked to the pathophysiology of several neuropsychiatric diseases. The reduction in the dendritic spine density has been found in patients with mood disorder as well as in animal models of depression[2]. Various antidepressant treatments in animals have been shown to recover the spine density and neuritogenesis that were decreased by previous applications of chronic stress or certain neurotoxic manipulations [58,59]. The abnormal spine morphology and the subsequent alteration in receptor trafficking and synaptic function are also suggested in animal models of schizophrenia[52]. Furthermore, a postmortem study reported the reduction of dendritic spines and axon boutons in the auditory cortex of schizophrenic subjects[60].

The loss of dendritic spines is a common irregularity found in brains of patients suffering from neurodegenerative disease. It is suggested that dendritic spines become deformed, thus the number of synapses is eventually reduced during the progression of Alzheimer's disease. The reduction of synapses positively correlates with cognitive impairments caused by Alzheimer's disease[61]. In animal models of Alzheimer's disease, the plaque formation of β-amyloid associates with the alteration of dendrite structures, the loss of dendritic spines, and loss of synapses in hippocampal and neocortical pyramidal neurons[62,63]. A series of studies demonstrated that the reduction of striatal dendritic spines are consistently observed in rodent and primate models of Parkinson's disease as well as in patients suffering from Parkinson's disease[64,65].

Drug abuse is caused by the maladaptation of the brain reward circuit that leads to uncontrolled use of drugs. Although there is no enough experimental evidence relating drug addiction to structural plasticity of neurons in the circuitry, several studies demonstrate that drug-induced synaptic plasticity involves the induction of LTP [52]. It was reported that the drug-induced plasticity involves altered branching of dendrites as well as changes in the density or morphology of dendritic spines. Psychostimulants, such as cocaine, is shown to increase dendritic spines and neurite complexity in nucleus accumbens medium spiny neurons, ventral tegmental area dopaminergic neurons, and prefrontal cortex pyramidal neurons[66]. The structural remodeling of dendritic spines might partly explain the long-lasting or persistent addictive behaviors and craving seen after chronic uses of psychostimulants.

3-4. Sig-1Rs regulate cognition and memory

In as much as Sig-1Rs regulate synaptogenesis involving actin polymerization as well as plasticity of neurons, such as LTP, it can be expected that Sig-1Rs or their ligands may

ameliorate pathological conditions related to abrupt synaptogenesis and neuroplasticity. In fact, Sig-1R agonists have been shown to ameliorate cognitive impairments caused in animals[3,67]. For example, fluvoxamine, a SSRI possessing the potent Sig-1R agonist property, significantly improves the phencyclidine-induced cognitive deficit in mice via activation of Sig-1Rs, but not via inhibition of serotonin transporters[68]. Despite the small sample size, fluvoxamine similarly improves cognitive function of schizophrenic patients [69,70].

Juvenile rats (between P30 and P41) exposed in utero to cocaine exert a series of neurobehavioral impairments; these behavioral and psychomotor deficits likely involve architectural alterations of neuronal circuits in developing brains[68,69]. Pretreatment with the Sig-1R agonist igmesine and neuroactive steroid dehydroepiandrosterone reverses learning deficits in those animals; these effects are blocked by the Sig-1R antagonist BD1063[69]. Sig-1R agonists, including (+)-SKF-10,047, also reverse memory and cognitive impairments induced by the cerebroventricular infusion of β-amyloid(1–40) peptides in rats[70].

Recent evidence indicates that Sig-1R agonists possess the rapid antidepressant-like action. Sig-1R agonists, such PRE-084, UMB23, and UMB82, have been recently proven to exert antidepressant-like effects in the forced swimming test of mice[71]. Interestingly, it is shown that Sig-1R knockout mice exhibit a depression-like phenotype[72].

Having a line of evidence showing that Sig-1R ligands regulate higher-ordered brains functions, such as mood and memory, a goal of future studies should be to provide a clear causal relationship between the Sig-1Rs' modulation of cytoskeletal architectures and the antidepressant-like or anti-amnesic action of Sig-1Rs.

4. Roles of sigma-1 receptors in neuroprotection and neurodegeneration

4-1. Neuroprotective action of Sig-1R agonists

In vitro studies demonstrated that Sig-1R agonists exert potent cell protective effects in a variety of cells, such as primary cerebral neurons, retinal ganglion cells, and lens cells[9,25,26,73,74]. Knockdown of Sig-1Rs increases vulnerability of cells to β-amyloid 25–35, oxidative stress, ER stress, and glucose deprivation[19,24], supporting a notion that the cell protection is one of the primary biological actions of the Sig-1R[19,47,69]. Similarly, the robust neuroprotective effect of Sig-1R agonists is reported in animal studies. Sig-1R agonists, such as 4-phenyl-1-(4-phenylbutyl) piperidine (PPBP), prevent infarction induced by occlusion/reperfusion of the middle cerebral artery in animals[75]. The Sig-1R agonist PRE-084 also attenuates β-amyloid 25–35-induced lipid peroxidation in hippocampus[69]. The neuroprotective effect of Sig-1R agonists is blocked by Sig-1R antagonists[69]. These actions of Sig-1R agonists seem to partly involve the regulation of NMDA-evoked production of NO or intracellular Ca^{2+} homeostasis in the brain[75]. How exactly Sig-1R ligands normalize Ca^{2+} homeostasis, NO generation and oxidative stress are unclear at this moment. However, since Sig-1Rs are enriched at ER membranes and exert the innate chaperone activity therein, one of primary action sites of Sig-1Rs in promoting neuroprotection should be the ER.

4-2. ER stress and neurodegenerative disorders

Accumulation of misfolded or aggregated proteins is one of major causes of neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease[24]. Recent studies provide evidence that the ER dysfunction caused by overloading of misfolded proteins (i.e., ER stress) plays crucial roles in the progression of these diseases[24]. Accumulation of misfolded proteins at

the ER activates two highly conserved adaptive programs: so-called the unfolded protein response (UPR) and ER overload response (EOR). In mammalian cells, the UPR is induced by three ER stress sensor proteins IRE1, ATF6 and PERK[24]. The activation of IRE1 and ATF6 promotes the transcriptional upregulation of ER chaperones, whereas the activation of PERK promotes the inhibition of the global protein synthesis by inhibiting eIF-2α (Fig. 4). The EOR involves the ER stress-induced ROS formation and activation of NFκB (Fig. 4). The EOR is also activated upon virus infection[76].

Active forms of PERK and IRE1 measured by immunohistochemical stainings are increased in hippocampal neurons of postmortem brains of Alzheimer's disease[77]. β-Amyloids potentiate UPR-induced transcription of ER chaperones[78]. IRE1 and PERK pathways are also activated in the cellular model of Parkinson's disease using 6-hydroxydopamine or 1-methyl-4-phenyl-pyridinium in PC12 cell cultures[79]. Prolonged expression of α-synuclein in PC12 cells also upregulates ER chaperones and activates PERK[80].

It is still unclear how cytoplasmic protein aggregates caused by neurodegenerative disorders induce ER stress. However, recent studies suggest that causal protein aggregates seen in neurodegenerative disorders [e.g., mutants of presenilin, α-synuclein, and superoxide dismutase-1 (SOD1)] interact with specific molecules involved in the UPR to promote dysfunction of the ER. The presenilin-1 mutant that is linked to familial Alzheimer's disease is shown to downregulates the UPR by impeding the activation of IRE1. Since activation of IRE1 promotes cell survival, whereas chronic activation of PERK triggers cell death[24], the inhibition of IRE1 by the presenilin mutant leads to cell death[77]. On the other hand, α-synuclein appears to promote cell death by promoting long-lasting activation of PERK because α-synuclein-induced death is blocked by the inhibitor of the PERK pathway salubrinal (the selective inhibitor of eIF-2α)[80]. Another set of the studies demonstrated that the SOD1 mutant induces severe ER stress by physically associating with a subcomponent of ERAD[81]. Since the ERAD is a key system retrogradely translocating misfolded proteins from the ER to the cytosol for proteasomal protein degradation, the SOD1 mutant inhibiting ERAD leads to a massive accumulation of misfolded proteins in the ER[81].

4-3. Oxidative stress and neurodegenerative disorders

Overproduction of free radicals is strongly implicated in the pathophysiology of neurodegenerative disorders as substantiated by findings that the protein side-chains are modified either by reactive oxygen species (ROS) or reactive nitrogen species (RNS), or by the products of lipid peroxidation in brains of these disorders. In brains of Alzheimer's disease, iron (Fe^{2+}) and copper (Cu^{2+}) both capable of stimulating free radical formation are increased[82]. DNA oxidation and lipid peroxidation are often observed in brains of neurodegenerative disorders[82]. Oxidative stress and free radical formation impair bioenergetics and mitochondrial function, as well as molecular chaperone capability to refold or dispose misfolded proteins. Specifically, the dysfunction of mitochondria may lead to depletion of ATP, reduced sequestration capability of cytoplasmic Ca^{2+}, and decreased capability to detoxify superoxide free radicals[23]. Chronic oxidative stress induces aggregation of pathogenic proteins such as α-synuclein[82]. Oxidation in the ER (e.g., the disulfide-bond formation) also contributes to oxidative stress and cytotoxicity related to neurodegenerative diseases[24].

Multiple factors seem to be involved in generation of free radicals in neurodegenerative disorders. More attention is recently paid to the metal-induced radical formation. α-Synuclein or β-amyloid *per se* generates hydroxyl radicals in the presence of Fe^{2+}[82]. Glutamate excitotoxicity has been also linked to free radical formation in neurodegenerative disorders[83]. Microglia-derived inflammatory neurotoxins also play a principal role in

formation of free radicals in brains of neurodegenerative disorders including HIV-associated dementia[8]. Antioxidants (glutathione, vitamins, flavonoids, and several dietary extracts) have been suggested as possible agents useful for the prevention and treatment of neurodegenerative disorders[82].

A number of studies demonstrated that Sig-1Rs or Sig-1R ligands regulate several above-mentioned processes involved in the pathophysiology of neurodegenerative disorders, which include protein folding, free radical formation, mitochondrial Ca^{2+} mobilization, glutamate toxicity, HIV-induced inflammation, and lipid peroxidation[8,20,26,48,84]. It is not clear yet how exactly Sig-1Rs regulate these variety of cellular events related to oxidative stress. However, recent studies begin to provide some clues to explaining the molecular mechanism underlying the actions of Sig-1Rs (see the following section).

4-4. Neuroprotection by Sig-1Rs

The neuroprotective action of Sig-1Rs likely involves the innate chaperone activity of Sig-1Rs[19]. ER stress is shown to cause the rapid upregulation of Sig-1Rs. Overexpression of Sig-1Rs attenuates the activation of PERK and ATF6 signalings and promotes cellular survival[19]. Apparently, the upregulation of Sig-1Rs is a defensive element for cellular survival under ER stress. The Sig-1R is reported to be downregulated in the putamen of patients in the early stage of Parkinson's disease as well as in brains of Alzheimer's disease[85–87]. Lowered Sig-1Rs seen in these subjects might raise susceptibility of the brain to ER stress. Sig-1R agonists that gain the innate chaperone activity of Sig-1Rs may thus exert therapeutic potentials in treating stroke, Parkinson's disease and Alzheimer's disease.

Recent studies demonstrated that one of cellular protective action of Sig-1Rs is mediated by ROS-dependent transcriptional upregulation of antiapoptotic protein Bcl-2[25,47]. ROS accumulation caused by knockdown of Sig-1Rs induces downregulation of Bcl-2 by activating the transcriptional factor NF-κB, the negative regulator of *bcl-2* transcription. Knockdown of Sig-1Rs promotes upregulation of p105, the precursor of NF-κB, as well as the conversion of p105 to the active form of NF-κB p50[47]. Conversely, overexpression of Sig-1Rs blocks the activation of NF-κB[49].

Correctively, recent findings suggest that the primary action of Sig-1R chaperones may be to regulate ER stress and mitochondrial function. But, the regulation of the two intracellular organelles and their communications seems to greatly contribute to the suppression of ROS and oxidative stress. As consequences, ROS-related downstream signalings that include many gene transcripts work collaboratively toward prevention of apoptosis and inflammation. Future studies need to elucidate details of each step of molecular events involved in this blue print.

5. Case reports, clinical trials, and brain imaging studies of sigma-1 receptors

5-1. Clinical targets of Sig-1R ligands: from the past to present

Since the prototypic Sig-1R ligand SKF10047 was found in the 1980s to possess the psychotomimetic action, the antipsychotic potential of Sig-1R ligands had been extensively examined[6–8]. During the 1990s, Sig-1R ligands were synthesized mostly to develop new drugs for the treatment of schizophrenia. However, after the cloning of the Sig-1R gene, molecular biological approaches were introduced in research, and emerged findings uncovered the unexpected relationship of Sig-1Rs to a variety of human diseases, including

depression, stroke, Alzheimer's disease, drug addiction, idiopathic pain, HIV infection and cancer[3,8,10,14,17,26,36,84].

5-2. Schizophrenia

Five Sig-1R compounds, panamesine (EMD57445), eliprodil (SL82.0715), rimcazole (BW234U), BMY14802 (BMS181100), and DuP734, had been introduced to clinical trials of schizophrenia[5,88–92]. BMY14802 (BMS181100) exacerbated acute psychotic symptoms in some acute schizophrenic patients[93]. Both rimcazole (BW234U) and eliprodil (SL82.0715) showed the efficacy to ameliorate negative symptoms such as depression and anergia in schizophrenia, however, exacerbated acute positive symptoms in some cases[91,94]. Although panamesine (EMD57445) had a positive result in treating positive symptoms of schizophrenia in one clinical study[89], two other clinical trials failed to replicate the similar efficacy[88,90,95]. DuP 734, the antagonist of both Sig-1R and serotonin 5-HT$_2$ receptor, was introduced into a phase I clinical trial, but the trial discontinued before entering a phase II[92,95]. Collectively, these findings suggest that Sig-1R ligands may not possess the potent antipsychotic action against positive symptoms of schizophrenia, but possibly useful for ameliorating certain negative symptoms of schizophrenia[5]. Recently, it was reported that fluvoxamine, a SSRI possessing a potent Sig-1R agonist activity, improves negative symptoms and cognitive deficits of schizophrenic patients who are under the antipsychotic treatment[69,70]. Binding assays using post-mortem brains of schizophrenic patients found the reduction of sigma binding sites in occipital, temporal, frontal, and temporal cortexes as well as in the cerebellum[96]. Another study reported the increase of sigma-binding sites in the cingulate cortex[97]. Among four case-control association studies, three studies failed to find significant associations between alleles of the Sig-1R gene [G-241T/C-240T and Gln2Pro (A61C)] and schizophrenia[98].

5-3. Depression and anxiety

Recent animal and human studies demonstrated a tight link between Sig-1Rs and higher-ordered brain functions, such as mood and cognition[5]. It is noteworthy that some clinically used antidepressants possess affinities for Sig-1Rs within the nM-Ki range. Opipramol is a tricyclic antidepressant currently used in Europe. Opipramol is a high-affinity Sig-1R agonist with weak affinities for H$_1$, sigma-2, 5-HT$_2$, and D$_2$ receptors. Opipramol lacks affinities for serotonin and noradrenalin reuptake sites[99]. Opipramol is effective in treatment of depressive mood, somatization, anxiety, and sleep disturbance[100]. Fluvoxamine is a SSRI used world-widely for treatments of depression, generalized anxiety disorder, and obsessive-compulsive disorder. Fluvoxamine, in contrast to other SSRIs, shows a superior efficacy in treating psychotic depression[101–103]. The combination therapy of fluvoxamine with antipsychotic drugs improves negative symptoms of schizophrenia, whereas the combination with the SSRI paroxetine does not[69,70,104,105]. It is proposed that these unique therapeutic profiles of fluvoxamine may be related to its high affinity for Sig-1Rs[101]. Afobazole, a selective Sig-1R ligand, is an anxiolytic drug launched in Russia in the early 2000s[106].

The Sig-1R serves binding sites of neurosteroids. It is reported that serum dehydroepiandrosterone (DHEA) and DHEA-sulfate are altered in patients with depression[107]. Studies also demonstrated that fluvoxamine increases neurosteroid allopregnanolone in the cerebrospinal fluid of patients with depression[108]. Administration of DHEA is shown to associate with the improvement of symptoms of major depression or dysthymia[109–112]. Whether the antidepressant-like action of neurosteroids in humans involves Sig-1Rs, as demonstrated in many animal studies[3], however needs further studies for confirmation.

Igmesine is the first Sig-1R agonist introduced to clinical trials of functional diarrhea and depression[113,114]. The clinical trial of depression moved further into the phase III, however the antidepressant effect failed to be confirmed in the large sample scale[114]. Recently, three Sig-1R ligands, OPC14523, YKP10A, and cutamesine (SA4503), completed phase II clinical studies[115–117]. Although OPC14523, a derivative of antidepressant trazodone, caused some improvement in major depression in phase II clinical trials, the effect failed to reach statistical significance. Interestingly, however, OPC14523 was found to improve sexual function of depressed patients enrolled in the trials. Now the effect is tested in phase III trials[118]. Cutamesine (SA4503), the selective and potent Sig-1R agonist, had been introduced in two phase II clinical trials aiming to depression and post-stroke neurological disturbances, respectively[117].

5-4. Neurodegenerative disorders

In the early 2000s, Sig-1Rs in conscious human brains were first time visualized by PET scanning using the tracer [^{11}C] SA4503 (e.g., [85]). Usefulness of [^{11}C] SA4503 for diagnosis of Parkinson's disease is now under the investigation[85]. A PET study using [^{11}C] nemonapride showed a significant increase of Sig-1R–binding sites in cerebellum of patients suffering from levodopa-induced dyskinesia[119].

A binding assay using post-mortem brains and PET scans suggested the decrease of sigma-binding sites in brains of Alzheimer's disease (AD)[86,120]. But, the validity of the data from PET studies must take a caution because donepezil taken by some subjects possesses a potent Sig-1R agonist property[121]. Interestingly, memantine, a novel AD medication, also binds to Sig-1Rs although its affinity might not be high enough to interact with Sig-1Rs at its therapeutic dose[122]. One study suggests that the haplotype TT-241–240P2 of the Sig-1R gene, which could lead to reduction of Sig-1R transcription, might be a protective factor against AD[123]. However, the other study failed to replicate this finding[124].

Sig-1R agonists carbetapentane and dextromethorphan (DM) are clinically used antitussive drugs. DM is also used for treating pseudobulbar affect (PBA) caused by ALS or multiple sclerosis (MS)[125]. PBA is a disorder characterized by uncontrollable disproportionate outbursts of laughing and/or crying. DM is also expected to ameliorate brain damages caused by stroke, neurosurgery and ALS[126]. A recent double-blind placebo-controlled trial with DM suggested that DM could reduce phantom pain, sedation, and analgesic requirements in cancer patients[127]. It has not been confirmed if these clinical effects of DM involve its action on Sig-1Rs.

We have to mention one more time about the recent genetic study, which has discovered a tight association between Sig-1R gene mutations and FTLD-MND [29]. This finding provides enormous implication of Sig-1Rs in the pathophysiology of human neurodegenerative disorders. The study found that, among a particular Australian pedigree (Aus-14), carriers of mutations at the UTR of the Sig-1R gene all suffer from FTLD, indicating the mutations may serve as a specific marker for a prediction of FTLD. Importantly, mutations that either increase or decrease the transcription of Sig-1Rs can both cause neuronal damages by inducing inclusion bodies composed of heterogeneous nuclear ribonucleoproteins in vitro. The specific brains regions and some motor neuron subcomponents appear to need to set the Sig-1R level within a precise range to cope with misfolded proteins. Since some other causal mutations of FTLD have been discovered (e.g., proglanulin, VPC)[29], the mutations of the Sig-1R gene may not be, however, always necessary for the onset of FTLD. These causal mutations and others related to neurodegenerative disorders phenotypically similar to FTLD (i.e., ALS) are all known to lead to dysregulation of protein sorting and degradation that often cause the ER dysfunction. The unexpected convergence in the concept of the Sig-1R derived from this clinical study

(i.e., the gene study of FTLD) and from basic studies (e.g., the identification of the Sig-1R as an ER chaperone) now begins to elucidate a clear picture of the pathophysiological implication of Sig-1Rs in human diseases.

5-5. Drug addiction and Alcoholism

In spite of substantial preclinical studies demonstrating roles of sigma receptors in drug abuse, so far only two clinical studies have been published in this regard (both of them are gene-association studies)[128,129]. This might be partly due to fewer activity or intention of pharmaceutical industries in introducing therapeutic drugs targeting drug abuse and alcoholism.

One gene-association study reported a link of Sig-1R polymorphisms to alcoholism[128]. The distribution of the Sig-1R gene polymorphisms was analyzed in 307 alcoholic and 302 control subjects. The frequencies of the A-485 allele and the TT-241–240/Pro2 haplotype in the 5'-upstream region, which lower transcriptional activity of the Sig-1R gene, were significantly higher in control subjects compared with alcoholic subjects[128]. The result suggests that A-485 allele or TT-241–240/Pro2 haplotype that lowers the expression of Sig-1Rs might be a possible protective factor against alcoholism. In the animal studies, Sig-1R antagonists, such as BD1047 and BD-1063, are shown to block the ethanol-induced conditioned place preference and ethanol intake in animals[130]. Further, in an animal study, the sigma-1 receptor agonist 2-(4-morpholino) ethyl 1-phecylcyclohexane-1-carboxylate (PRE-084) is shown to enhance the ethanol-induced conditioned place preference in a dose-dependent manner[130]. These findings raise a possibility that the increased Sig-1R expression and/or their hyperactivation may underlie a part of the mechanism involved in alcohol dependence. In contrast, a recent study reported that ethanol-naive Sardinian alcohol-preferring rats or Wistar rats which were withdrawn from chronic alcohol treatments showed reduced Sig-1R mRNAs in the nucleus accumbens[131]. It is unclear at present whether the downregulation of Sig-1R transcripts is caused by compensatory gene regulation or by withdrawal of ethanol.

The association of the Sig-1R polymorphism GC-241–240TT or A61C (Gln2Pro) with methamphetamine dependence was also examined in a Japanese population with 143 methamphetamine abusers and 181 control subjects[129]. This study reported no significant association between these Sig-1R polymorphisms and methamphetamine abuse, although the rate of the CC genotype of A61C tended to be higher in methamphetamine abusers who had experienced spontaneous relapse of methamphetamine psychosis[129]. The sample size in this study is limited to draw a conclusion. However, future studies, particularly those focused on methamphetamine psychosis, would warrant to be investigated. In an animal study Sig-1Rs are shown to be upregulated in the midbrain of rats that self-administered methamphetamine, but not in those that received passive injections of methamphetamine in a non-contingent manner[132]. A highly selective sigma-1 antagonist MS-377 was shown to abolish the methamphetamine-induced behavioral sensitization in rats[133]. These preclinical studies support a notion that upregulation/hyperactivation of Sig-1Rs in specific brain regions may be involved in development of drug addiction.

There are also numerous animal studies demonstrating a relationship between cocaine dependence and Sig-1Rs[6]. Many of them suggest a potential of Sig-1R antagonists ameliorating cocaine intoxication, dependence, and craving, although those effects have not been tested in clinical studies. Cocaine at clinically relevant concentrations can interact with Sig-1Rs and upregulate Sig-1Rs in animals[45]. The critical step to move forward this research aspect should be therefore to introduce Sig-1R antagonists to studies using non-human primates or human subjects.

6. Conclusion

In the last decade, the considerable progress has been made in the sigma receptor research. Unveiled signaling cascades downstream of Sig-1Rs elucidate a variety of molecular functions of Sig-1Rs regulating cellular redox, neuronal survival and synaptogenesis. The novel ligand-operated property of the Sig-1R chaperone may enable a variety of interventions by which stress-related cellular systems are pharmacologically controlled. Highly selective, high-affinity Sig-1R ligands (i.e., ligands with pM affinity, high subtype selectivity) have been recently developed together with reliable in vivo and in vitro functional assays. In light of the recent great advance in Sig-1R research and accumulating evidence promising therapeutic potentials of Sig-1R ligands, it is encouraged to introduce more selective Sig-1R ligands in clinical studies, and test their efficacy in the treatment of human diseases.

7. Expert opinion

Originally identified as a binding site separated apart from the opioid receptors[134], the Sig-1R now stands as a protein with its own unique properties. Among those properties are: (1) The sequence of the Sig-1R does not share with any of the mammalian proteins, thus preserving a fundamental function that probably could not be substituted by any other proteins; (2) Sig-1Rs are distributed not only in the CNS but also in many important peripheral organs[20], likely playing important physiological roles not only in the CNS but also in the periphery; (3) As a chaperone protein, the Sig-1R possesses a great degree of tolerance not only for the binding of various classes of ligands but also for perhaps a diverse kind of client proteins to be fully unveiled in the future, allowing regulations by multiple drugs for different diseases; (4) The translocation property of Sig-1Rs allows them to modulate proteins not only at the ER-mitochondrion contact but also at the plasma membrane where many ion channels, receptors, and kinases were found to be regulated by Sig-1Rs, rendering Sig-1Rs as a unique interorganelle signaling modulator in the living system[12].

Despite recent advances on our understanding of the Sig-1R, more research into the receptor is needed. Foremost of all is that the molecular properties unveiled from cell lines need to be translated into the organ level including of course the brain, the liver, heart, pancreas, spleen, lungs, and kidney. In doing so, one must keep in mind that client proteins for Sig-1Rs may differ from organ to organ and the signaling cascades related to Sig-1Rs may differ as well. Apparently, the role of Sig-1Rs in each organ must firstly be carefully examined and its relation to disease state can thus be established. Within the brain, as Sig-1Rs are implicated in so many CNS diseases, the exact role of Sig-1Rs in each disease must be fully clarified and the precise mechanism be teased out. An obvious question of course is: how can a protein like Sig-1R be involved in so many diseases in the brain? The answer to this question given recently in a speculation in a review article[12] deserves a serious thought and should be subjected to in-depth tests in the future. The speculation was that diverse CNS diseases may result in conformational instability of different ion channels or receptors which then demand the assistance of Sig-1Rs to correct the conformation of respective protein to fight thus against the particular disease. In this regard, it is tempting to speculate that Sig-1R associated ligands may have therapeutic potentials in protein conformation diseases. Another important question concerning the action of Sig-1Rs is how Sig-1Rs can apparently activate the function of some client proteins (e.g., D_1 receptor; [135]) while block that of others (e.g., Na^+, K^+, SK channels; [12]). As those client proteins of Sig-1Rs are related to many diseases, the exact mode of action of Sig-1Rs against each client protein needs to be investigated and clarified. Final question on the Sig-1R would be their exact localization in the synapse. Most publications showed the post-synaptic

localization of Sig-1Rs. However, recent data suggest the pre-synaptic localization of Sig-1Rs[37]. Thus, potential actions of Sig-1Rs at both sides of the synapse exist and should be examined in the future.

We are now on a much better position to let the scientific communities know what Sig-1Rs may do in the living system but we are far away from pinning down the exact function of Sig-1Rs in a particular disease. Although pharmacological tests have shown some promises in certain or in fact many diseases by utilizing Sig-1R ligands, the society will benefit more if the precise mechanism of action of Sig-1Rs is fully established at least in a couple of diseases in the foreseeable future.

Acknowledgments

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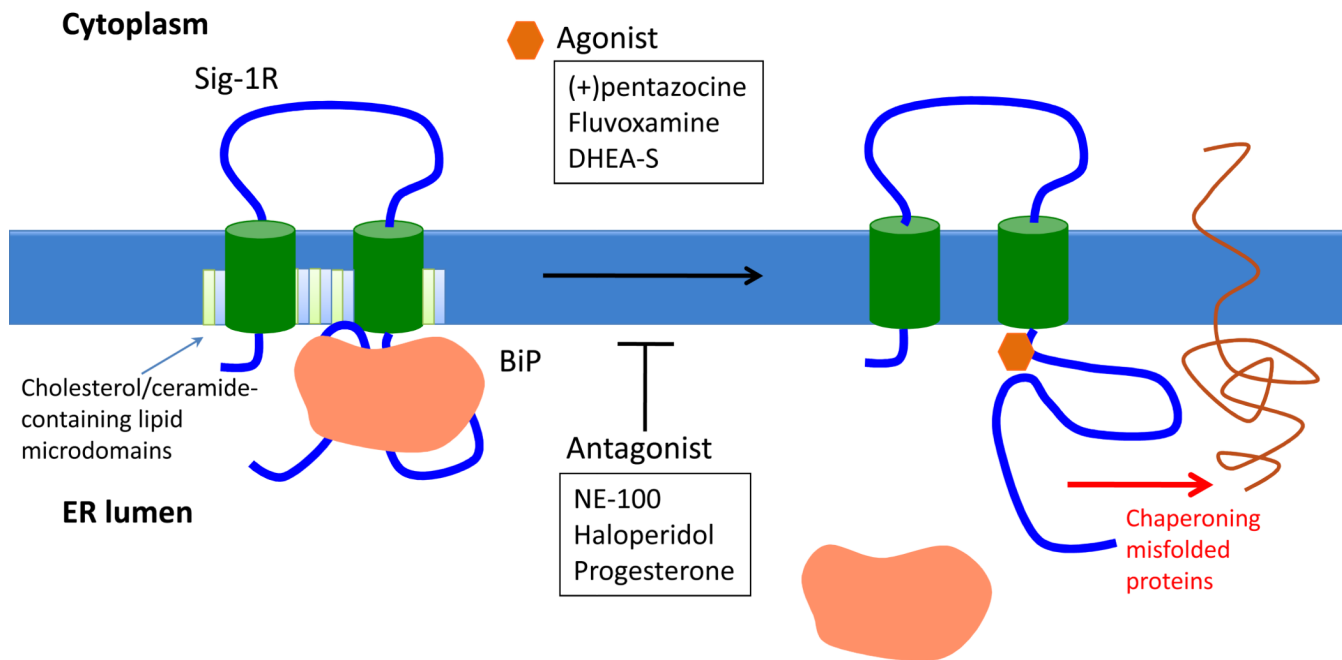
Fig. 1. Ligand-operated regulation of the Sig-1R chaperone
The Sig-1R is an integral membrane protein comprised of two transmembrane domains and a long C-terminus residing in the ER. Sig-1Rs are highly clustered at the cholesterol and ceramide-rich lipid microdomains at the specialized ER subdomain (e.g., mitochondria-associated ER membrane: MAM). At the dormant state, the Sig-1R forms a protein complex with another ER chaperone BiP. Sig-1R agonists or the depletion of ER Ca^{2+} promotes the dissociation of the Sig-1R from BiP, thus maximizing the chaperone activity of the Sig-1R. Sig-1R antagonists reinforces the association, thus block the action of Sig-1R agonists. Recent studies suggest that the second transmembrane domain and the domain residing at the C-terminus are juxtaposed to form a ligand-binding site of Sig-1R ligands.
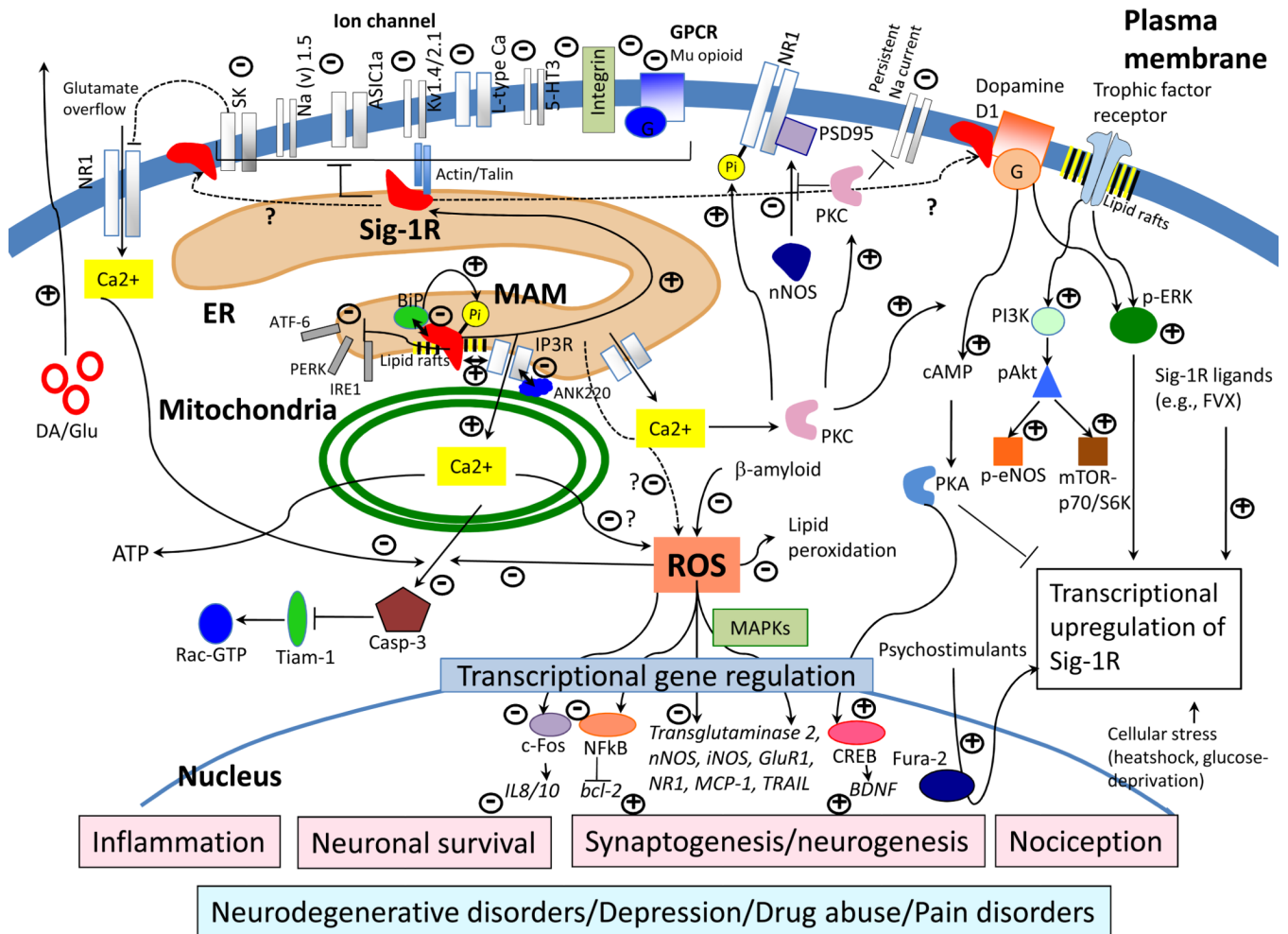
Fig. 2. Signaling cascades of the Sig-1R

Signaling pathways explored in the last 5 years are summarized. Signaling cascades of the Sig-1R fall into three categories: 1) the rapid action involving physical protein-protein interaction or signaling molecules (e.g., chaperone activation, Ca^{2+} signaling, regulation of kinase activity or protein phosphorylation), 2) transcriptional regulation of gene expression downstream of the Sig-1R signaling (e.g., ROS-induced NFκB activation, CREB-induced transcription), 3) stress- or ligand-induced upregulation of Sig-1Rs. Overexpression or knockdown studies highlighted that the Sig-1R protein level per se, even in the absence of exogenous ligands, affects several cell death/survival signalings. It is not fully clarified how Sig-1Rs translocate from ER to plasmalemmal ER subdomains or to plasma membrane to physically associate with plasma membrane proteins such as ion channels and dopamine D1 receptors (see text "The unique subcellular localization of Sig-1Rs"). Note: data summarized are obtained from various cell types and brain regions. They are depicted together for simplicity. (+), pathways/molecules potentiated by Sig-1R expression or Sig-1R activation by agonists; (−), pathways/molecules inhibited by Sig-1R expression or Sig-1R activation by agonists. (-->), activatory pathway; (--I) inhibitory pathway.
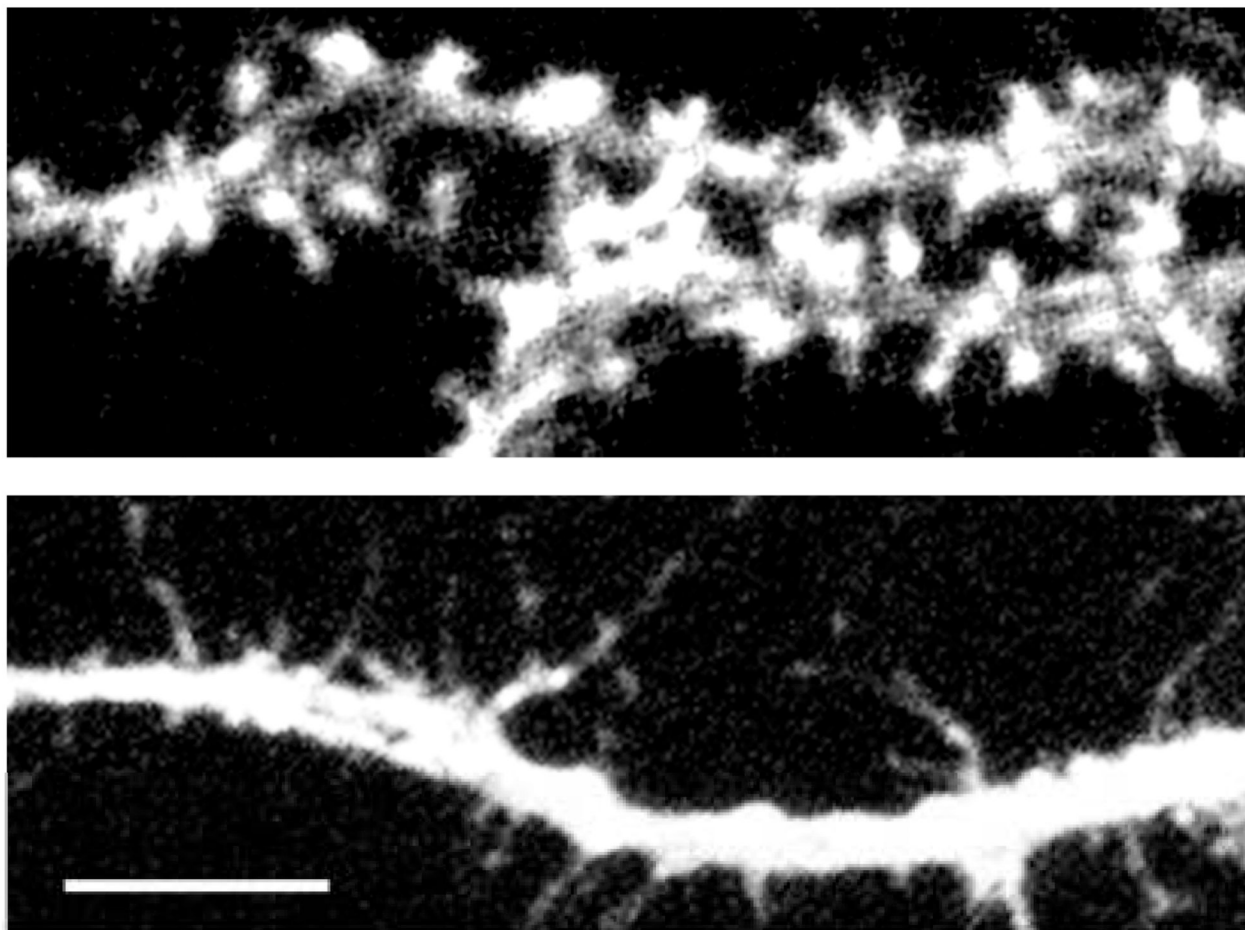
21 DIV hippocampal neuron
Top: siCon
Bottom: siSig-1R
scale bar= 5μm

Fig. 3. Aberrant synaptogenesis induced by knockdown of Sig-1Rs
Rat primary hippocampal neurons at DIV 14 were infected with the adeno-associated virus (AAV) particles carrying GFP cDNA together with either the control siRNA or Sig-1R siRNA. Dendrite morphology was examined at DIV 21 with a confocal microscope by exciting cytoplasmic GFP. In contrast to the control forming mature mushroom-like spines at the dendrite, the dendrite infected with Sig-1R siRNA protrudes long thin filopodia lacking spine-head structures.
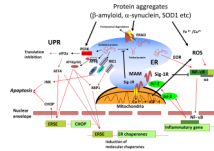
Fig. 4. Neuroprotective actions of Sig-1Rs

Under ER stress, unfolded proteins accumulated in the ER activate ER sensor proteins PERK, ATF6 and IRE1. IRE1 and ATF6 promote upregulation of ER chaperones via activation of the ER stress response element (ERSE). Activated PERK phosphorylates eIF2α, thus leading to the inhibition of translational initiation of protein synthesis. This process is collectively called the unfolded protein response (UPR). Under prolonged ER stress ER stress, sensor proteins activate cell death pathways, including JNK and CHOP. The ER overloading response (EOR) induced by ER stress activates NF-κB, which leads to the downregulation of Bcl-2. Although protein aggregates formed in neurodegenerative disorders are often, but not always, deposited in the cytoplasm, they destruct UPR and ERAD (ER-associated degradation) systems by interacting with specific ER proteins. β-Amyloid protein and α-synuclein form protein aggregates as well as induce oxidative stress by directly activating ROS generation. ER chaperone Sig-1Rs are upregulated under ER stress to attenuate accumulation of misfolded proteins and EOR. Sig-1Rs promote cell survival in part by transcriptionally upregulating Bcl-2 expression via inhibition of the ROS/NFκB pathway. Blue and red arrows indicate cytoprotective and cell death pathways, respectively.

Table 1

Sigma-1 receptor ligands

Sigma-1 receptor ligands used in recent preclinical studies (2007~2010)

1   Synthetic compounds

- AC927

- Anisamide: *Utilized for siRNA delivery to carcinoma cells*

- 4-(*N*-benzylpiperidin-4-yl)-4-iodobenzamide (4-IBP): *Agonist inhibiting cancer migration*

- *N*-benzyl-*N*'-(2-hydroxy-3,4-dimethoxybenzyl)-piperazine (BHDP): *Protects liver against ischemic damages*

- BD-1047: *Prototypic antagonist*

- BD 1063: *Prototypic antagonist*

- BMY14802: *Antagonist*

- 3-(4-(4-cyclohexylpiperazin-1-yl)butyl)benzo[d]thiazole-2-(^{3}H)-thione (CM156)

- Ditolylguanidine (DTG): *With both sigma-1 and sigma-2 affinities*

- E-5842

- Etrahydro-*N,N*-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2–73): *Agonist with potent neuroprotective activity*

- 1-*N*(2',6'-dimethylmorpholino)3-(4-t-butylpropylamine) (fenpropimorph): *fungicides*

- Metaphit: *Irreversible sigma receptor antagonist*

- Methyl(1R,2S/1S,2R)-2-[4-hydroxy-4-phenylpiperidin-1-yl)methyl]-1-(4-methy lphenyl) cyclopropanecarboxylate [(+/−)-PPCC]: *Agonist with anti-amnesic action*

- NE-100: *Selective antagonist*

- OPC-14523: *Agonist with the 5-HT$_{1a}$ affinity. Rapid antidepressant-like action*

- (+)Pentazocine: *Prototypic selective agonist*

- 4-phenyl-1-(4-phenylbutyl)-piperidine (4PPBP): *Selective agonist with potent anti-stroke action*

- PRE-084: *Selective agonist*

- SA4503: *Selective agonist with anti-stroke and antidepressant properties*

- SM 21: *Sigma-2 antagonist*

- Rimcazole: *Low affinity antagonist*

- (+)-SKF10047: *Non-selective agonist*

1   Endogenous compounds or natural extracts from plants

- Berberine: *Alkaloid isolated from Berberis aristata Linn; antidepressant-like action*

- Cocaine: *Agonist with a low μM affinity*

- Crocins/picrocrocin: *Saffron herbal extracts*

- DHEA-sulfate: *Agonist, endogenous neurosteroid*

- DHEA: *Agonist endogenous neurosteroid. The affinity for Sig-1Rs is lower than DHEA-sulfate.*

- D-erythro-sphingosine and sphinganine: *Endogenous sphingolipids*

- *N,N*-dimethyltryptamine: *Endogenous trace amine*

- Progesterone: *Antagonist*

1   Clinically used drugs

- Afobazole (5-ethoxy-2-[2-(morpholino)-ethylthio]benzimidazole dihydrochloride): *Anxiolytic drug*

- Carbetapentane: *Cough suppressant*

- Dextromethorphan (DM): *Antitussive drug; DM-quinidine (Q) therapy is effective in reducing pseudobulbar affect in ALS and multiple sclerosis*

- Donepezil: *Sigma-1 agonist; acetylcholine esterase inhibitor used in Alzheimer's disease*

- Fluvoxamine: *Clinically used SSRI; Sig-1R agonist*

- Sertraline: *Clinically used SSRI with a putative Sig-1R antagonist property*

- Haloperidol: *Clinically used antipsychotic; potent, but non selective sigma antagonist*

- Haloperidol-metabolite II (reduced HP, 4-(4-chlorophenyl)-alpha-(4-fluorophenyl)-4-hydroxy-1-piperidinebutanol): *In contrast to haloperidol, having higher selectivity to Sig-1Rs*

- Memantine: *A novel Alzheimer's disease medication blocking NMDA glutamate receptors*

- Zonisamide: *Anti-parkinson drug approved in Japan*

The most recent imaging ligands (2007~2010)

- (+/−)-2 [1'-benzyl-3-(3-fluoropropyl)-^{3}H-spiro[[2]benzofuran-1,4'-piperidine], WMS-1813

- ^{11}carbon-labeled piperidine ring of *N*-[omega-(6-methoxynaphthalen-1-yl)alkyl] derivatives

- (+)-2-[4-(4-iodophenyl)piperidino] cyclohexanol [(+)-pIV]

- spirocyclic 3-(3-fluoropropyl)-2-benzofurans

- [99mTcN(PNP)Pip-DTC]

- [^{11}C]SA4503: *First PET tracer for human Sig-1Rs*

- 1-*N*-(2',6'-dimethyl-morpholino)-3-(4-azido-3-[^{125}I]iodo-phenyl)propane ([^{125}I]IAF): *For photo-affinity labeling*

- 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-(2-iodophenylpropyl)piperazine: *For SPECT*

- PB183

- (+)-2-[4-(4-iodophenyl)piperidino]cyclohexanol [(+)-pIV]

- [^{18}F]1-(3-fluoropropyl)-4-((4-cyanophenox)methyl) piperidine

- 1-cyclohexyl-4-[3-(6-hydroxynaphthalen-1-yl)propyl]piperazine: *Fluorescent sigma-1 ligand*

- 3-iodo-4-azidococaine ([^{125}I]IACoc): For photoaffinity labeling

- (+)-2-[4-(4-iodophenyl) piperidino] cyclohexanol

Newly developed high affinity Sig-1R ligands (2007~2010)

- Tic-Hydantoins

- 3-benzazepin-1-ols: *With NR2B glutamate receptor antagonistic action*

- piperazinebutyrates

- pyridylpiperazines

- (±)-2-(1-Benzyl-piperidin-4-yl)-1-benzothiopyran-4-one Oxalate

- *N*-(benzofuran-2-ylmethyl)-N'-(4'-(2''-fluoroethoxy)benzyl)piperazine

- *N,N*-dibutyl-3-(4-nitrophenyl)propylamine

- aza-trishomocubane

- 1'-benzyl-3-methoxy-^{3}H-spiro[[2]benzofuran-1,4'-piperidine]: *Agonist*

- spiro[[2]benzopyran-1,4'-piperidines]

- 6-allyl-6,8-diazabicyclo[3.2.2]nonane derivatives

- 1-cyclohexylpiperazine and 3,3-dimethylpiperidine derivatives

- 3-[[1-(4-chlorobenzyl)piperidin-4-yl]methyl]benzo[*d*]oxazol-2(^{3}H)-one: *Sig-1R affinity=0.1 nM, sigma-2 affinity=427 nM*

- Sila-haloperidol: *Higher selectivity for Sig-1R than haloperidol; silicon haloperidol*

- phenylethylene diamines: *Anti-cocaine action*

- 1'-Benzyl-6-methoxy-1-phenyl-4,6-dihydrospiro[1*H*–furo[3,4-*c*]pyrazole-4,4'-piperidine]: *Sig-1R affinity=0.5 nM, sigma-2 affinity=1750 nM*

- 1-benzyl-6'-methoxy-6',7'-dihydrospiro[piperidine-4,4'-thieno[3.2- c]pyran]

- 1-benzyl-4-(3-phenylpropyl)piperazine

- 3-(4-(3-(bis(4-fluorophenyl)amino)propyl)piperazin-1-yl)-1-phenylpropan-1- ol: *Dopamine transporter/Sig-1R ligand*

- 1-benzyl-4-phenylpiperidine-4-carbonitrile oxalate: *Sig-1R affinity=0.4 nM, sigma-2 affinity=2657 nM*

- trishomocubane analogues TC1 (*N*-(3'-fluorophenyl)ethyl-4-azahexacyclo [5.4.1.0(2,6).0(3,10).0(5,9).0(8,11)]dodecan-3-ol)

Table 2

Clinical studies using Sig-1R ligands or compounds with Sig-1R affinities

The efficacy of Sig-1R antagonists[§] and ligands in the treatment of schizophrenia

Compound	Study design	Study phase	Efficacy (responders/total number of patients)	Reference
BMY 14802 (BMS181100)	single-blind	II (discontinued)	No	Gewirtz 1994
rimcazole (BW234U)[§]	open single-blind	II (discontinued)	Yes (7/19) Yes (8/12)	Davidson 1982 Chouinard and Annable 1984
	open		Yes (3/6)	Guy 1983
	open		Yes (5/12)	Schwarcz 1985
	double-blind		No	Borison 1991
eliprodil (SL82.0715)[§]	open	[*1]	Yes (negative symptoms) (2/7)	Modell 1996
panamesine (EMD57445)	open open open	II (discontinued)	Yes (5/12) Yes (4/7) Yes (1/5)	Frieboes 1997 Huber 1999 Müller 1999
DuP734[§]	open	I (discontinued)	No	Gilligan 1994

The efficacy of Sig-1R agonists or antidepressants with Sig-1R affinity in the treatment of affective disorders or related symptoms				
Compound	Study design	Study phase	Efficacy (responders/total number of patients)	Reference
Igmesine (CL-1019, JO-1784)	Open DBT, RCT	III (discontinued)	Yes (18/30) No	Pande 1999 Pande 1999
opipramol	DBT, RCT DBT, RCT	Clinically used	Yes (63%, /307) Yes (statistically/72)	Möller 2001[*] Gerlach 2002[**]
Fluvoxamine	DBT	Clinically used	Yes (/30)	Silver 1998[***]
	DBT		Yes (/25)	Silver 2000[***]
	DBT		Yes (/53)	Silver 2004[***]
			Yes	Gatti1996[****]
			Yes	Stahl SM 2005[****]
			Yes	Serretti A 2000[****]
dehydroepiandrosterone sulfate (DHEAS)	Open DBT, RCT DBT, RCT	Clinically used for other purpose	Yes (5/6) Yes (5/11) Yes (60%, 9/15)	Wolkowitz 1997 Wolkowitz 1999 Bloch 1999

The efficacy of Sig-1R agonists or antidepressants with Sig-1R affinity in the treatment of affective disorders or related symptoms				
Compound	Study design	Study phase	Efficacy (responders/total number of patients)	Reference
OPC-14523		II		Paschos 2009
YKP10A		II		Amsterdam 2002
Cutamesine (SA4503)	DBT, RCT	II		Matsuno 1996

*
1 Developed as a NMDA blocker and introduced to phase II for Parkinson's disease

DBT ; double-blind trial, RCT ; randomized controlled trial

*
Used for generalized anxiety disorder;

**
used for sleep disturbance;

***
used for negative symptoms of schizophrenia;

****
used for psychotic depression