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Sigma-1 receptor as a potential pharmacological target for the treatment of neuropathology

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Abstract

Sigma receptors are usually classified as a separate class of intracellular receptors. Among them the sigma-1 receptor has been the most studied regarding its pharmacological applications. This receptor with average or high affinity binds a wide range of chemical compounds of very different structural classes and a variety of therapeutic and pharmacological properties. The sigma-1 receptor is a trans-membrane protein placed in the endoplasmic reticulum (ER), which regulates the function of inositol-3-phosphate receptor, stabilizing the calcium signaling between ER and mitochondria. There are studies that the sigma-1 receptor is involved in the formation of many neurological and psychiatric conditions. It is assumed that the sigma-1 receptor acts as a sensor of normal calcium operation. The studies over the recent years have shown the role of the violation in calcium signaling in the pathogenesis of Alzheimer's and Huntington's diseases. In particular, changes in calcium homeostasis of the endoplasmic reticulum lead to the break of synaptic connections in the neurons. Thus, the sigma-1 receptor holds promise in application as a potential therapeutic target for the treatment of neuropathological diseases.

Keywords: Sigma-1 receptor; Endoplasmic reticulum; Calcium signaling; Chaperone activity; Neuropathology.

Introduction

Numerous data of preclinical studies performed on various models of memory impairment indicates that agonists of sigma-1 receptors show much promise as drugs to treat cognitive dysfunction [1,2,20,61–63]. Adjusting the excitability of the neuronal plasma membrane through the sigma-1 receptor probably plays a key role in preventing neurologic diseases.

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Generally, it can be claimed with certainty that the sigma-1 receptor acts as an intracellular modulator:

between the endoplasmic reticulum (ER) and the mitochondria,
between the ER and the cell nuclei,
between the ER and the membrane,
as well as a modulator of intracellular signaling.

Since the sigma-1 receptor binds a wide range of chemical compounds of very different structural classes with various therapeutic properties, it is of great interest for pharmacology. The researchers of the Laboratory of Molecular Neurodegeneration (LMN) of the Peter the Great St. Petersburg Polytechnic University support the calcium hypothesis of neuropathology. This hypothesis indicates that the disruption of calcium signaling plays a key role in the emergence and development of neurodegenerative diseases. The sigma-1 receptor, which is the subject of this review, regulates the function of the inositol trisphosphate receptor, thus stabilizing calcium signaling between mitochondria and the endoplasmic reticulum.

Consequently, our greatest interest in studying the sigma-1 receptor is in revealing its biophysical role in forming neurological and psychiatric conditions, as well as in regulating intracellular concentrations of calcium ions and calcium signaling.

The purpose of this review is to analyze the information in the current literature regarding the sigma-1 receptor, its structure and biophysical role in cells, and the participation of this receptor in normal and pathological processes.

Sigma receptors were originally considered a type of opioid receptors, but now they are classified as a separate class of receptors with unique structure and the set of binding ligands. Among this type of receptors, the sigma-1 receptor is the most pharmacologically studied.

The sigma-1 receptor has a protective function in different tissues. The effect of this receptor is mediated by regulation of cell metabolism, suggesting its involvement in various neuropsychiatric diseases [1]. These receptors regulate various ion channels, including potassium, calcium, chlorine, and NMDA-receptors, release various neurotransmitters, provide lipid transport and brain-derived neurotrophic factor (BDNF) signaling, myelination, neurito- and synaptogenesis, which shows high therapeutic potential for the sigma-1 receptor ligands. The modulating effect of sigma-1 receptors on neurotransmitter systems includes enhancing the glutamatergic, cholinergic, and serotoninergic neurotransmission. In contrast, the activation of sigma-1 receptors reduces the intensity of noradrenaline release and gamma-aminobutyric acid. An increase or a decrease of the calcium current due to the effect of sigma-1 receptors explains why the selective agonists of these receptors can modulate a wide range of neuronal effects, including a key mechanism by which sigma-1 receptors influence learning and memory processes [2].

Molecular biology of the sigma-1 receptor

This receptor is a highly conserved mammalian protein [3,4]. Sequence alignment showed that the protein sequence is 30% identical (the homology is 67%) to yeast C8-C7 sterol isomerase, but the receptor itself does not exhibit this enzymatic activity [5].

The gene of the sigma-1 receptor is located on chromosome 9p13, known due to its being associated with psychotic disorders [6]. The sigma-1 receptor, with its small size (223 amino-acid residue), binds with medium or high affinity to a wide range of chemical compounds of very different structural classes with various pharmacological and therapeutic properties. Among its ligands there are such compounds as benzomorphans (SKF-10047, pentazocine, dextromethorphan), antipsychotics (haloperidol), antidepressants (fluvoxamine), steroids (progesterone), antihistamines (chlorpheniramine), nuclear hormone receptor ligands (tamoxifen), Ca^{2+} channel antagonists (verapamil, emopamil), antifungals (fenpropimorph, tridemorph) and drugs of abuse (methamphetamine, cocaine, and N,N-dimethyltryptamine) [7]. However, the sigma-1 receptor knockout mice are viable as well as fertile, and do not exhibit any apparent changes in the phenotype except for a reduced hypermotor activity in response to SKF-10047 stimulation compared to wild-type mice. This fact supports the idea that the sigma-1 receptor is involved in response to psychostimulatory actions [8].

Sigma-1 receptors are widely spread in the central nervous system, liver, kidneys, and lungs, in the endocrine, immune and reproductive tissues [9]. This receptor is a transmembrane protein specifically located in ceramide- and cholesterol-rich lipid microdomains associated with the mitochondria of the ER membrane. It regulates the function of the inositol-3-phosphate receptor, stabilizing calcium signaling between the ER and the mitochondrion. It has been shown that the sigma-1 receptor forms Ca^{2+}-regulating trimeric complex with ankyrin-B and the inositol-3-phosphate receptor in NG-108 neuroblastoma cells [10].

Additionally, by adjusting the levels of reactive oxygen species, the sigma-1 receptor controls the levels of Rac GTPase in the plasma membrane, thus responsible for the formation of spines in the hippocampus, which is a central brain region responsible for memory formation [11]. Through regulating the level of reactive oxygen species the sigma-1 receptor also activates NF-κB transcription factor, which controls the expression of the Bcl-2 anti-apoptotic protein [7], and is therefore involved in supporting neuronal life. It was demonstrated on cortical cell cultures that SA4503, a sigma-1 receptor agonist, increased the number of surviving cells following oxidative stress through the suppression of the MAP kinase pathway and the expression of glutamate receptors [12].

Even though the sigma-1 receptor does not directly interact with the G-protein [13], physical and functional connections have been revealed between the sigma-1 receptor and the cloned opioid μ-receptor (which binds the G-protein) [14]. These interactions, which occur only in a form of the sigma-1 receptor related to the antagonist, manifested as significantly facilitated activation of the G-protein by the agonist of μ-receptor DAMGO, which is confirmed by the enhancement (observed in vivo) of morphine-induced analgesia by the antagonists of the sigma-1 receptor.

Functional activity and location of the sigma-1 receptor in a cell depend on the state of the cell, on the stimulation of the receptor by ligands and the level of calcium concentration in the ER. The sigma-1 receptor may be both active and inactive. The most recent studies indicate that this receptor interacts with chaperones, and is itself an ER chaperone [3]. When inactive or stimulated by antagonists (for example, NE-100 or haloperidol), the sigma-1 receptor is linked to another ER protein, a BiP chaperone [10]. When stimulated by agonists (for example, cocaine or pentazocine) at a saturation concentration, or if subjected to prolonged cellular stress caused by, for example, hypoglycemia or depletion of calcium reserves in the ER under the action of thapsigargin, the sigma-1 receptor translocates either to ER regions near to the plasma membrane, or directly into the plasma membrane [15, 16].

Overexpression of the sigma-1 receptor also leads to its increased translocation to the plasma membrane [17]. It was demonstrated in a mouse model [18] that chronic alcohol consumption causes increased expression (and therefore, possibly, translocation to the plasma membrane) of the sigma-1 receptor in the brain. At the same time, a recent study by Yao et al. [19] has revealed that cocaine causes the sigma-1 receptor to translocate from the ER to the lipid rafts of the plasma membrane, where chemokines CCL2 are induced in microglia via Src-kinase activation. It is also shown that overexpression of the sigma-1 receptor in cortical neurons increases the binding of the tyrosine kinase receptor B and phospholipase C [20].

After translocating to the plasma membrane, the sigma-1 receptor interacts with various ion channels, receptors and kinases [21]. In fact, it was demonstrated using the patch-clamp on pituitary gland cells that pentazocine, which is a sigma-1 receptor agonist, inhibits the outward current of potassium ions (K^+), and this phenomenon can be reversed by the sigma-1 receptor antagonist NE-100 [22]. In addition to direct physical interaction and regulation of the activity of voltage-gated K^+ channels in mouse nerve terminals of the posterior lobe of the pituitary gland [23], the sigma-1 receptor regulates the activity of the K^+ channel in rat hippocampal slices, intracardiac neurons and cancer cells [24]. The sigma-1 receptor ligands modulate several types of presynaptic Ca^{2+} channels in rat sympathetic and parasympathetic neurons [25]. The sigma-1 receptor also modulates the NMDA receptor activity [26] and affects synaptic plasticity through the small-conductance Ca^{2+}-activated K^+ channels [27]. The sigma-1 receptor has been shown to modulate cardiac voltage-gated Na^+ channels in HEK293 and COS- cells, as well as in neonatal mouse cardiomyocytes [28]. SKF-10047, a sigma-1 receptor agonist, inhibits calcium ion currents in cultured retinal ganglion cells. Direct association between the sigma-1 receptor and the L-type Ca^{2+}-channel was performed using immunoprecipitation [29].

There is also data indicating that the sigma-1 receptor regulates neurotransmitter release in dopaminergic, serotonergic and cholinergic transmission, and is involved in cell differentiation, cellular responses to inflammation, and in pathogenesis of extrapyramidal disorders [21].

Interestingly, the sigma-1 receptor was detected in the extracellular space of NG-108 cells exposed to cocaine, indicating that the receptor possibly acts as a chaperone in the extracellular space [7].

The structure of the sigma-1 receptor

The sigma-1 receptor is an integral membrane receptor, and it is predominantly localized in the ER membranes associated with mitochondria [16].

Even though the detailed atomic structure of the receptor has not yet been determined, a number of studies have been focused on establishing the protein topology and on mapping its active site. Initially, the

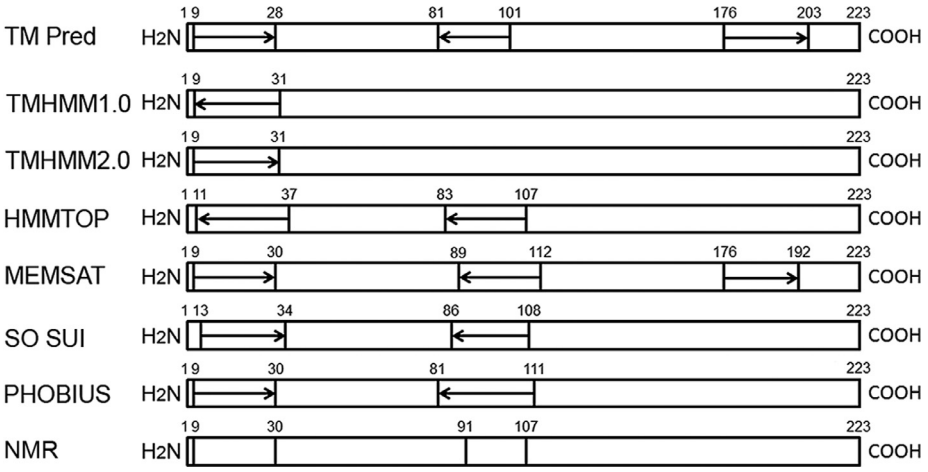

Fig. 1. Topological models of the sigma-1 receptor, constructed on the basis of the amino acid sequence of the receptor using a variety of predictive algorithms: TM Pred [31], TMHMM [32, 33], HMMTOP [34], MEMSAT [35], SO SUI [36] PHOBIUS [37], and the NMR method. H_2N and COOH are, respectively, the N- and the C-terminals of the amino acid sequence; the numbers correspond to the serial numbers of amino acid residues; arrows indicate the orientation of the transmembrane helix in the biological membrane (→ away from the cytoplasm, ← towards the cytoplasm) (see Fig. 2).

sigma-1 receptor has been characterized as a type I transmembrane protein with a single transmembrane domain [30]. Currently, a fairly large number of experimental data indicates that there are two alpha-helical transmembrane domains. This data was obtained via bioinformatic analysis, molecular simulation, epitope mapping techniques, limited proteolysis, and NMR spectroscopy.

The number and localization of transmembrane domains are different and depend on the specific algorithm chosen for predicting hydrophobic domains based on the amino acid sequence (Fig. 1) [31–37]. Most algorithms indicate the presence of two or three hydrophobic regions (see. Fig. 1). The first two domains have been identified as highly ordered transmembrane alpha-helices (TM1, TM2). The second transmembrane helix has amphipathic properties [38]. Amino acids 91–109 and 176–194 contain highly conserved sequences homologous to the yeast and fungal sterol C8–C7 isomerase. Due to their homology, these sequences were named steroid-binding domain-like I and II (SBDLI and SBDLII) (Fig. 2a) [39].

The results of epitope mapping and limited proteolysis are also consistent with the results of computer analysis of the sequence. To date, two alternative topological models have been proposed, differing from each other by the orientation of receptor insertion into the lipid bilayer (Fig. 2b and c) [16, 23]. Aydar et al. [23] proposed a topological model of the sigma-1 receptor, where two transmembrane domains of this receptor, TM1 and TM2, are connected in the extracellular space by a loop of about 50 amino acid residues, while its N- and C-termini are oriented towards the cytoplasm (see. Fig. 2b) [23]. The C-terminal segment extends for approximately 125 acids, and the N-terminal is relatively short and includes only 10 amino acids.

An alternative topological model was proposed by Hayashi and Su; according to them, the sigma-1 receptor is localized in the ER membranes, while its N- and C-termini are facing the ER lumen (see. Fig. 2c) [16].

A di-arginine (R7E/R8E) motif, which is a signal for the retention of the receptor in the ER membranes, is located at the N-terminal of the protein [30,40].

There are currently several known full-length splice variants of the full-length sigma-1 receptor. One of the forms is a variant lacking exon 3 (amino acids 119–149) [41]. Another form that has been described is a truncated sigma-1 receptor the alternative splicing of whose mRNA results in the formation of a premature stop codon (12-kDa variant) [42]. It is known that both forms are incapable of binding ligands. Their functional significance also remains unknown.

It has been shown that the isolated transmembrane (amino acids 1–116) and C-terminal (amino acids 116–223) receptor domains also lack the ability to bind ligands, even though some of the receptor's functions are preserved (in particular, the ability to activate the Ins3P receptor or the chaperone activity of the C-terminal segment) [16, 43]. Significantly, the isolated C-terminal domain is also localized in the ER membranes, which is consistent with the presence of a third hydrophobic membrane-bound region near SB-

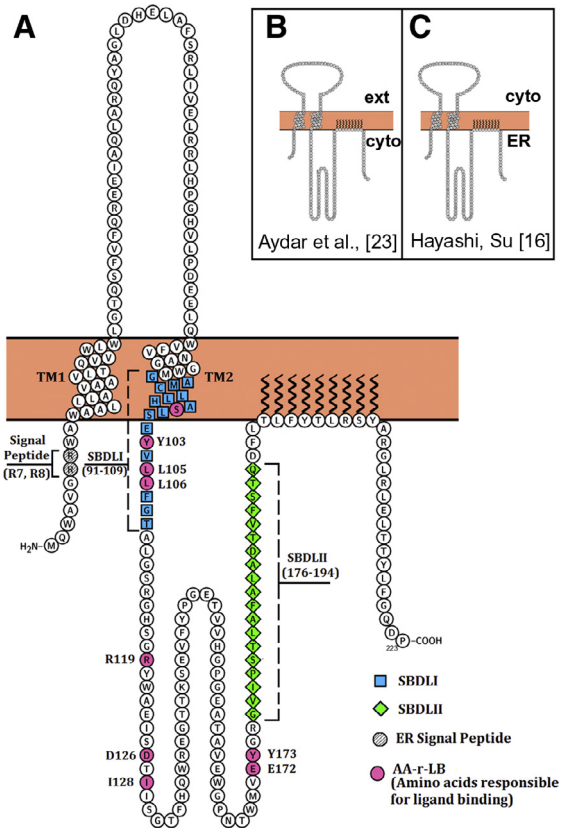

Fig. 2. Estimated structure of the sigma-1 receptor and the amino acid residues responsible for binding its ligands, according to data obtained by different methods: site-directed mutagenesis and tagging by photosensitive ligands (a), and also the orientation of membrane receptors according to epitope tagging [23] (b) and limited proteolysis [16] (c). Ext is the extracellular space; Cyto is cytoplasm; ER is the lumen of the endoplasmic reticulum; TM1 and TM2 are the highly ordered transmembrane alpha-helices; SBDLI and SBDLII are the steroid-binding domains I and II; ER Signal Peptide is the ER signaling sequence, AA-r-LB are the amino acid residues participating in binding the ligands of the sigma-1 receptor. The numbers correspond to the serial numbers of amino acid residues.

DLII. NMR spectroscopy showed that residues 198–206 correspond to this membrane-bound region [44].

Recently, Ortega-Roldan et al. determined the secondary structure of the sigma-1 receptor by NMR spectroscopy [44]. The hydrophobic TM2 domain is located around residues 91–107, whereas the amphipathic membrane-bound region is within the range of residues 198–206. The SBDLI and SBDLII segments (see. Fig. 2a) have been identified as alpha-helical. The loop facing the cytosol is formed by several short alpha-helical regions and loop sections. The same group of authors has studied conformational changes occurring in the C-terminal segment (amino acids 112–223) through binding to the ER chaperone protein GRP78/BiP [38], which have been shown to affect virtually all amino acid residues of the sigma-1 receptor.

At present, it has been established through site-directed mutagenesis, photoaffinity labeling and molecular simulation techniques that all the domains of a compact receptor-binding site are in one way or another involved in its formation (see. Fig. 2).

The first experiments in mapping the active site using site-directed mutagenesis allowed to identify critical residues in the second transmembrane domain for the ligand-binding function of the receptor: S99, Y103, L105 and L106 [45]. Using specific synthetic ligands with photo-reactive labels, it was shown that the binding site is formed by SBDLI residues 91–109 surrounding the critical nitrogen atom detected in all agonists and antagonists specific for the sigma-1 receptor [46-49]. Additionally, SBDLII amino acids 176–194 are involved in the formation of the binding site, surrounding the phenyl ring of the ligand. Chen et al. [49] described in their paper [49] the cocaine binding site in the sigma-1 receptor and, using photosensitive 3-iodo-4-azidococaine and radiosequencing, identified the D188 residue (located in the SBDLII region) as one of the key amino acids involved in the formation of a ligand-binding site.

The C-terminal sequence 209–223 is crucial for maintaining the structure of the active site, with its deletions leading to loss of the ligand-binding properties [49].

The carboxyl terminus of the first transmembrane domain TM1 is also involved in the formation of the binding site through close interaction with the SBDLI and SBDLII regions located within a distance of 8 Å from each other [46,50]. Thus, the hypothetical spatial organization of the ligand-binding site of the sigma-1 receptor is based on the intramolecular juxtaposition of the TM1/SBDLI segments with the SBDLII region.

A recent series of papers described building a model of the sigma-1 receptor and mapping its active site by in silico methods and site-directed mutagenesis [51,52]. The initial model was constructed by homology modeling (PDB 3CIA, 1I24, 2Z2Z, 2Q8I), while its non-homologous part (the N-terminal segment) was constructed de novo. The computer simulation results are in good agreement with the currently available experimental data, and the model itself has been used to design and develop new, more specific synthetic ligands of the sigma-1 receptor [53,54]. Mapping of the active site allowed to identify the key residues involved in pentazocine binding, a sigma-1 receptor agonist. Aspartic acid residue D126 forms a crucial connection, a salt bridge to the nitrogen atom of the

pentazocine molecule; E172 forms a hydrogen bond with the hydroxyl group of the ligand; the R119, I128, Y173 residues form a hydrophobic pocket of the active site. Residue mutations in the SBDLII region had little effect on the binding of ligands, but the C-terminal segment of residues 200–223 turned out to be necessary for stabilizing the structure of the binding site. This model is in good agreement with the hypothesis about the presence of the binding site involving all of the receptor domains.

There is evidence that the sigma-1 receptor is functionally active and capable of binding ligands only in oligomeric state [55,56]. The first macromolecular forms of the sigma-1 receptor (molecular masses of 97, 130 and 147 kDa) were detected in the microsomal membranes of the rat liver using radioiodinated photoaffinity labels [46]. Further evidence of the existence of the sigma-1 receptor in various forms (both monomeric and oligomeric) was also obtained using spectral FRET imaging in living COS-7 cells [57].

In vitro experiments with the purified recombinant MBP-S1R fusion protein showed that only oligomeric forms of the sigma-1 receptor (hexamers, tetramers, and octamers) are capable of binding the tritiated agonist [3H]–($^{+}$)-pentazocine, while the monomers are functionally inactive [55]. Haloperidol, which is a well-known antagonist, promotes high-molecular oligomeric forms, but pentazocine, which is an agonist, stabilizes the dimers of the sigma-1 receptor [57].

The ability to oligomerize is associated with the structural features of the sigma-1 receptor. Two presumed GxxxG dimerization motifs were found in the receptor sequence [56,58,59]. The first of them is located in the TM2 domain (residues 87–91), while the second one is in the C-terminal region of SBDLII (residues 108–112). It is possible that the first motif mediates the dimerization of the sigma-1 receptor, and the other is responsible for the formation of high molecular weight oligomers. All point mutations in the oligomerization domain (GGWMG, residues 87–91) led to a significant decrease in the expression of the receptor in cells and also to a shift of the oligomeric forms of the receptor toward monomers [55]. The truncated form of the sigma receptor-1 (residues 1–122) is capable of forming heteromers with the full-length version of the receptor, negatively regulating the function of the full-length version [42].

Chu et al. proposed a model in which the sigma-1 receptor forms a homodimer or an oligomer containing dimers, with the 1:1 binding stoichiometry of ligand to dimer of the sigma-1 receptor [56]. In contrast with this model, a number of other computer simulation studies demonstrate that it is possible for ligands to bind to a monomeric form of the sigma-1 receptor, which corresponds to the stoichiometry of one ligand per one receptor [51–53].

There was an attempt to explain the physiological meaning of the balance between the oligomeric and the monomeric forms of the sigma-1 receptor by the hypothesis that oligomerization of the sigma-1 receptor regulates its ligand-mediated functions [57]. Presumably, the sigma-1 receptor ligands can influence the kinetics of the interaction between the receptor and the so-called client proteins (ion channels, and others) by varying the ratio between the oligomeric and the monomeric forms and shifting the balance towards the former.

To date, the sigma-1 receptor is identified as a highly dynamic molecule capable of forming homomeric complexes for maintaining the multiple functions of the receptor.

Further research using high-precision methods of structural biology, such as X-ray crystallography and NMR spectroscopy is necessary in order to answer the questions about the localization and the organization of the ligand-binding site more precisely, and to determine the stoichiometry for different ligands binding to the sigma-1 receptor.

The role of the sigma-1 receptor in neuropathology

Depression is known to be one of the neuropsychological disorders, in which the sigma-1 receptor plays a key role. In this case, there is an observed dysfunction of the brain structures modulated by monoaminergic systems, such as the frontal cortex and the hippocampus. Some antidepressants have the properties of the sigma-1 receptor ligands, modulating many neurotransmitter systems, which involves the antidepressant effect associated with the sigma-1 receptor. Indeed, the sigma-1 receptor agonists exhibit a significant antidepressant effect in various models [60]. Currently, there is evidence that these receptors affect mood by enhancing the serotonergic and glutamatergic neuronal functions, as well as due to the neurotrophic actions. The enhanced activation of serotonergic neurons in the dorsal raphe nucleus is an important effect of the sigma-1 receptor agonists. The activation of the serotonergic transmission under the influence of such agonists starts as early as after two days of treatment, while the clinically significant changes induced by the inhibition of serotonin reuptake appear only two or three weeks after the antidepressant administration started. A quick serotonergic effect of the sigma-1

receptor agonists suggests an earlier onset of the antidepressant action compared to traditional antidepressants. Moreover, a combination of the selective sigma-1 receptor agonist pramipexole and the sertraline antidepressant in sub-effective doses exhibits a synergistic antidepressant-like effect in an experimental model of depression [61]. In patients suffering from depression, there is a decrease of NMDA receptors in the prefrontal cortex and hippocampus. An experimental model of depression (olfactory bulbectomy in rats leading to a decrease in the number of NMDA receptors) is accompanied by a behavioral deficit resembling agitation, loss of interest and cognitive dysfunction typical for clinical depression. The sigma-1 receptor agonists improve the behavioral deficit and also increase the expression of NMDA receptors. These findings suggest a link between depression and two types of receptors: NMDA and sigma-1 [20].

Along with the modulating role of the sigma-1 receptors in the glutamatergic and serotonergic transmission associated with depression, they have an additional mechanism of action related to neuroplastic processes. The neurotrophic effect of some antidepressants due to the induction of the neuronal growth factor can be regulated by the sigma-1 receptors [62]. A high binding affinity of fluvoxamine in therapeutic doses for the sigma-1 receptors in the brain indicates that some effects of this antidepressant are connected precisely with the receptors in question.

Thus, the analysis of preclinical studies allows to suggest possible additional clinical effects of the antidepressants with the properties of the sigma-1 receptor agonists. Clinicians are focused on such phenomena as the improvement of cognitive abilities, the acceleration of the antidepressant action; the neuroprotective effect [63].

There is also data pointing to the physiological role of the sigma-1 receptor in motor neurons. In particular, it was found that the E102Q mutation in the receptor leads to an autosomal recessive form of juvenile paralysis [64]. Motor neurons of the spinal cord die in the course of this disease. Life expectancy is significantly reduced in mutant mice with the deleted gene of the sigma-1 receptor showing symptoms of paralysis, and the paralysis symptoms occur earlier than in the mice expressing the sigma-1 receptor. This suggests that this receptor inhibits the development of degenerative processes even in mice [65]. The exact role of the sigma-1 receptor has not yet been determined, but different hypotheses have been proposed.

An immunohistochemical study revealed that the sigma-1 receptor is localized underneath the cholinergic boutons. It has been previously proven that two types of potassium channels, Kv2.1 and SK are located in the postsynaptic membrane of motoneuronal cholinergic synapses. These channels release potassium ions from cells and thus reduce motoneuronal excitability, which is particularly important because motor neurons are the first to die in stress conditions. It was shown that the sigma-1 receptor ligands were shown to affect the activity of the Kv2 and SK-type potassium channels [21]. This regulation possibly exists in motor neurons as well. The sigma-1 receptor can influence potassium channels either by direct interaction or through a chain of interacting proteins. Thus, the sigma-1 receptor is capable of interacting with the inositol triphosphate receptor located on the ER membrane, while the receptor's activators lead to a significant increase in calcium release from the ER to the cytosol. Calcium activates calmodulin, which, in turn, directly activates the SK channel in the plasma membrane. Besides, calmodulin can influence the Kv2.1 channel by activating calcineurin, which causes the dephosphorylation of the channel and leads to its further activation [66]. Thus, both potassium channels can be modulated by the activation of the sigma-1 receptor via a cascade of protein interactions. The sigma-1 receptor also plays an important role in other regions of the central nervous system. For example, retinal ganglion cells were shown to die in larger numbers when the sigma-1 receptor was knocked out than ganglion cells of healthy animals. Mice that were injected with amyloid peptide and thus acquired symptoms of Alzheimer's disease exhibited a significantly improved performance in memory tests [67]. Studies using positron emission tomography showed that the sensitivity of the sigma-1 receptors does not change in normal aging, which contrasts with the age-dependent decline in cholinergic, glutaminergic and dopaminergic reception. However, a decrease (a loss by 26%) in sigma-1 receptors was found in the hippocampal CA1 region in patients suffering from Alzheimer's disease compared with healthy people. Moreover, this reduction correlated with the degradation of pyramidal neurons [68]. It has recently been discovered that agonists of these receptors can suppress microglial activation. As a result, the inflammatory component of neurodegenerative diseases is reduced.

Furthermore, recent studies have revealed the role of impaired calcium signaling in the pathogenesis of Alzheimer's and Huntington's diseases. In particular, changes in calcium homeostasis in the ER result in the disruption of synaptic connections in neurons [69]. The sigma-1 receptor is assumed to act as a

sensor of normal calcium homeostasis. Recently, this receptor was also discovered to be a potential target for pridopidine [70]. This drug has shown some positive effects in the third phase of treatment of Huntington's disease, and is currently assessed for potential use in further clinical trials [71]. Based on the observed effects of the drug in experiments on animals, pridopidine is considered by researchers as a dopamine 'stabilizer'. However, the precise molecular mechanism of its action on the dopamine receptors is yet to be clarified [72].

Conclusion

This review considered the specifics of the composition and structure of the sigma-1 receptor. We discussed possible biophysical mechanisms of the regulation of the receptor and of its involvement in various cellular processes, as well as its role in the development of various neuropathologies. Additionally, we have described potential applications of the sigma-1 receptor as a therapeutic target in the treatment of this type of diseases.

Given the broad opportunities for using the sigma-1 receptor as a protein-based therapeutic target, the Laboratory of Molecular Neurodegeneration (LMN) of the Peter the Great St. Petersburg Polytechnic University is conducting comprehensive biophysical studies on the role of the sigma-1 receptor in the context of neuropathological research, using such methods as computer modeling, X-ray crystallography, and confocal microscopy.

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Remark

This remark has been added at the stage of proofs. While this article has been in press the first crystal structure has been determined by Schmidt et al. For further reading on the structure of sigma-1 receptor, see

H.R. Schmidt, S. Zheng, E. Gurpinar, A. Koehl, A. Manglik, A. Kruse, Crystal structure of the human $\sigma 1$ receptor, Nature 532 (7600) (2016) 527-30.

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