

Review

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Review

Pharmacological and Pathological Implications of Sigma-1 Receptor in Neurodegenerative Diseases

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Abstract: Originally identified as a potential receptor for opioids, sigma-1 receptor is a class of intracellular receptors expressed in various tissues including neurons. As a resident protein in the mitochondria-associated endoplasmic reticulum (ER) membrane, sigma-1 receptor has been found involved in various biological and disease processes including stress responses, neurotransmission, and neurodegenerative diseases. Herein we discuss the history, structure, functions, and pharmacology of sigma-1 receptor and its pathological implications in neurodegenerative diseases.

Keywords: sigma-1 receptor; sigma receptor; TMEM97; neurodegenerative disorders; ER stress; Alzheimer's disease; amyotrophic lateral sclerosis

1. Introduction

Sigma receptors were discovered in the 1970s when the scientific community was actively exploring the mechanisms of action of opioids, focusing on their interactions with various receptors in the brain. W.R. Martin investigated the effects of various drugs, including opioids and opioid-like compounds, on the central nervous system. It was observed that SKF-10047, a congener of morphine, caused mydriasis, tachypnea, tachycardia, and mania in contrast with morphine, a mu receptor agonist, and ketocyclazocine, a kappa receptor agonist. Its unique binding profile did not align with the traditional opioid receptors known at the time—mu, kappa, and delta, suggesting the existence of a previously unidentified receptor type. The "sigma" classification, derived from the Greek letter σ , is used to denote its distinct binding properties [1]. This discovery has sparked considerable interests in finding additional pathways through which the opioid drugs could exert their effects.

The 1980s and 1990s were pivotal for sigma receptor research. Studies by Tam and Cook (1984) pointed out that the effects of sigma ligands could not be reversed by naloxone, an opioid antagonist, which is a defining feature of opioid receptors, suggesting a pharmacological distinction from opioid receptors [2]. It was eventually accepted that sigma receptors are not a typical opioid receptor due to their unique binding sites, affinities, and pharmacological profile, as well as their naloxone insensitivity [3].

Later, based on pharmacological profiles, binding characteristics, and tissue distribution patterns, sigma receptors were categorized into sigma-1 receptor (S1R) and sigma-2 receptors (S2R) [4]. For instance, the sigma-1 receptor has a high affinity for (+)-pentazocine, while the sigma-2 receptor does not. Conversely, certain ligands distinguish sigma-2 receptors by their higher affinity for these receptors compared to sigma-1 receptors. This differential ligand binding was one of the initial methods used to distinguish between the two receptor subtypes. In addition, the difference in molecular weight as determined by photoaffinity labeling studies and other biochemical techniques were noticed.

The cloning of the sigma-1 receptor in 1996 by Hanner et al. was a significant milestone, revealing its molecular structure and function [5]. The gene for the sigma-1 receptor encodes a protein that does not resemble any traditional G protein-coupled receptors but instead, actually shares some

characteristics with molecular chaperones. In contrast, the molecular identity of the sigma-2 receptor remained elusive until much later in 2017, with its gene revealing it to be distinct from sigma-1 receptor and involved in different cellular processes [6], setting a significant advancement in sigma receptor research.

Initially misconstrued as a variant of opioid receptors, sigma receptors have emerged as a distinct class of proteins, playing distinct roles in cellular signaling, neurophysiology, and pharmacology. Their discoveries have opened new avenues to understand the molecular underpinnings of various diseases and develop novel therapeutic strategies.

2. Sigma-1 Receptor: Structure, Functions and Pharmacology

The sigma-1 receptor is a novel protein localized to the endoplasmic reticulum (ER) that interacts with lipid rafts [1,7–9]. The first cloning took place in 1996 when it was found to be on gene 9p13 [5,10]. The sigma-1 receptor crystal structure was identified shortly thereafter [5,11–13], which is a homo-trimer with a unique transmembrane domain for each region [14,15]. Within this homo-trimer, oligomerization is notably increased with sigma agonists and decreased with antagonists [16]. Certain multi-level oligomers induce the ability to form heteromers with other receptors, such as the dopamine receptor [17,18]. With a molecular weight of 25kDa, it possesses no similarities to other known proteins in the genome [9,19].

Following the discovery of the sigma-1 receptor was the sigma-2 receptor, which is less researched, however it resembles similar properties of S1R due to binding patterns to SKF-10047 and its location within lipid rafts [7,20–22]. Most notably, sigma-2 receptor is potentially a putative binding site for progesterone receptor membrane component 1 (Pgrmc1) [23]. Eventually, the sigma-2 receptor was later identified as the known protein TMEM97 [6]. Currently, S1R and S2R are primarily differentiated based on ligand binding assays. H3(+) pentazocine has relatively selective affinity for sigma-1, whereas H3-DTG or H3-(+)-3-PPP combined with a sigma-1 masking agent, such as pentazocine, is selective for sigma-2 [24,25].

The sigma-1 receptor plays many roles within the cell. It can translocate between the ER, mitochondria, and cell membrane [26–29]. In addition, the sigma-1 receptor couples with G-proteins, ion channels, the IP3 receptor, and the glutamate receptor [29–31]. Specifically, it is expressed in multiple vital organs such as the heart, liver, and kidney as well as immune cells [32]. The sigma-1 receptor can bind a wide variety of ligands, such as antipsychotics, antidepressants, and neurosteroids [3,33]. Currently, it is suggested to play a role in cell survival, as tumors and other cancers show highly expressed levels of sigma-1 receptor. Furthermore, it is suggested to play a role in neuroprotection through acting as a molecular chaperone protein [8,34–37].

In the resting state, the sigma-1 receptor is under the classification of a mitochondria-associated-ER membrane domain (MAM), as it resides near the mitochondria in ceramide and cholesterol rich lipid microdomains with BiP, an ER chaperone protein [27,38]. Under times of cell stress, the ER becomes injured, causing the sigma-1 receptor to dissociate from BiP. Upon dissociation, it can bind IP3 receptors, leading to an increase in cell survival through calcium signaling between the ER and mitochondria. Previous testing has shown that sigma-1 receptor agonists increase this stress-like response, while antagonists cause the opposite effect [27].

Overall, the sigma-1 receptor is shown to play a non-regulatory role in normal conditions, but act as a chaperone protein in times of stress to benefit cell survival [30]. In addition to modulating the IP3 pathway, sigma-1 receptor is shown to interfere with dopaminergic and cholinergic transmission, manipulating the ion channels in these various families [39–42]. Here we review the pharmacologic and pathologic implications of the sigma receptors in the nervous system.

3. Sigma-1 Receptor in Nerve Injury

Injuries to the nervous system can take place with many mechanisms, such as mechanical trauma or an ischemic insult in both the central and peripheral nervous system [43–45]. When a nerve

undergoes injury, it has been studied that there is an increase in S1R expression [46]. S1R is theorized to play a protective role in ischemic stroke by preventing neural apoptosis and inflammation while increasing neurotrophic factors [47,48]. One of the key mechanisms in apoptosis following ischemic stroke is endoplasmic reticulum stress, which can be lessened with S1R activation [48,49].

Strokes are one of the most common causes of disability in the world, with the majority being ischemic [50]. Generally, the prognosis of a stroke can be derived from the extent of ischemia, which represents the amount of dead neural tissue [51]. There is hope that S1R agonism can reduce the size of an infarct and promote better outcomes [52]. Not only could S1R agonism result in a smaller infarct, but there are potential mechanisms to restore damage already done in white matter injury after a stroke [53]. Following an ischemic stroke, macrophages are critical for a process known as efferocytosis, which clears dead neurons from the infarct and induces neural repair and inflammation resolution [54]. The role of S1R in this topic has recently been unraveled, and studies show that S1R knockout (KO) models led to impaired macrophage function and worsened brain damage after ischemic stroke [55]. The functional outcomes from S1R agonism after stroke are not limited to functional outcomes but also cognition [56].

Strokes also carry the risk of damaging the blood-brain barrier (BBB) integrity and increasing permeability to substances otherwise unable to enter the brain [57]. S1R activation may attenuate this damage by inducing the BBB astrocytes to increase levels of glia-derived neurotrophic factor (GDNF) [58,59]. BBB integrity may be compromised due to pericyte detachment, which can also be ameliorated with S1R activation [60,61]. Another pathology seen in stroke is spreading depolarizations (SDs), which are depolarizations of neural cells due to a failure of ion homeostasis after an insult [62,63]. S1R agonists were able to resolve the SDs and promote neural survival and reduce apoptosis [64]. A rather unfavorable outcome of ischemic stroke is reperfusion injury, characterized by a worsening of damaged cells after blood flow is returned, causing inflammation and apoptosis [65]. Upregulation of S1R may promote favorable outcomes after reperfusion injury [66].

Interestingly, in models of traumatic brain injury (TBI), mice deficient in sigma receptors had better outcomes, such as less coordination impairments and neurological deficits after 1 year [67]. Other studies of TBI find that S1R agonism led to better neurological function, including restoration of blood flow and less brain edema, suggesting a biphasic role in TBI [68]. This paradoxical effect is perhaps due to long-term S1R activation resulting in unfavorable long term outcome but are beneficial in the acute phase. The acute phase of TBI is marked by inflammation, which is dampened with S1R activation [69]. Implications of S2R on TBI is much less studied, however modulation may result in more favorable outcomes [70]. As far as spinal cord injury, S1R activation resulted in effective recovery after a mechanical insult to the spine. This was done through reducing neuroinflammation and decreasing the amount of neural apoptosis and ferroptosis [71,72]. Ferroptosis is a rather novel mechanism for cell death related to the buildup of lipid oxidation products and has been described as an unfavorable mechanism resulting in neuronal cell death after injury [73,74]. Additional results concluded that ferroptosis was significantly upregulated after spinal cord injury [71].

4. Sigma-1 Receptor in Neurodegenerative Disorders

Sigma receptors are implicated in a variety of neurodegenerative disorders due to their functioning in calcium homeostasis, mitochondrial function, and oxidative stress regulation [29,75–77]. In fact, genetic polymorphisms related to S1R have been shown to influence development of Alzheimer's disease (AD) [78]. Other mutations of S1R, such as loss-of-function, have been linked to the development of amyotrophic lateral sclerosis (ALS) as well as frontotemporal dementia (FTD) [79,80]. This is perhaps due to the loss of long-term potentiation seen in S1R KO mice [81]. Other neurological disorders have had favorable outcomes with sigma-receptor modulation, and these include Huntington's Disease (HD), multiple sclerosis (MS), and Parkinson's Disease (PD) [82–84]. In recent years, the sigma-1 receptor has gained attention as potential therapeutic targets for mitigating

these diseases, among others [85]. The overlapping mechanisms of S1R mediated neuroprotection are summarized in Figure 1. Additionally, the utility of S2R ligands is rising in interest for their potential in providing neuroprotection [86].

S1R agonism has been linked to neuroprotection through mechanisms involving synaptic plasticity through brain-derived neurotrophic factor (BDNF) dependent mechanisms [87–89]. Other mechanisms for neuroprotection studied with S1R agonism include reduction of intracellular nitric oxide (NO) by inhibiting NO synthase [90,91]. Prevention of oxidative stress is another critical aspect to slow the development of neurodegeneration, and sigma-receptor ligands often act through this mechanism [92–94]. All these mechanisms play a central role in homeostatic plasticity, which is the stabilization of neural pathways, and loss of this plasticity is central to neurodegeneration [95,96]. Gross manifestations of neuroprotection have been studied in mouse models using modalities such as novel object recognition, showing favorable outcomes with sigma-1 agonism [97,98].

Neuroinflammation is another key factor in the progression of neurodegenerative disorders [99]. Downregulation of S1R has been shown to increase inflammation markers and induce dysregulation of the surrounding microglia [100]. S1R agonists and allosteric modulators have been shown to decrease neuroinflammation levels through reduction of microglial recruitment and inhibition of pro-inflammatory cytokines, and the resulting attenuation of gliosis has potential to slow cognitive impairment from various degenerative conditions, such as chronic epilepsy [101–104].

4.1. Sigma-1 Receptor in Alzheimer's Disease

Mitochondrial dysfunction is a hallmark of neurodegeneration in many of neurodegenerative disorders, including Alzheimer's Disease (AD) [105]. Restoration of mitochondrial stability is a sought-after avenue for S1R modulation [106]. S1R agonists, such as N, N-Dimethyltryptamine (DMT), have been shown to restore levels of S1R and preserve mitochondrial function. Chronic treatment with this ligand led general neuroprotection as well as a slowing of beta-amyloid accumulation, the hallmark of Alzheimer's Disease [107–112]. A similar effect is seen with pridopidine and PRE-084, other S1R agonists, which restored mitochondrial dysfunction through lowering levels of reactive oxygen species [82,113]. Agonists of S1R also had synergistic neuroprotective roles when combined with acetylcholinesterase inhibitors, the current treatment for AD [114]. Paradoxically, other studies have shown that MAM induction leads to increased amyloid-beta accumulation, which can be reduced with S1R downregulation [115].

Another critical hallmark in the development of AD is deposition of neurofibrillary tangles, characterized by hyperphosphorylated tau protein [116]. In healthy individuals, it has been discovered that S1R assists with maintaining normal levels of phosphorylation on tau proteins [117]. Additional studies show that the presence of functional S1R is imperative to ensure that the development of AD does not take place [118]. Less studied mechanisms to slow the progression of AD include their role in alleviating disruption of the BBB, which may be achieved through increasing levels of vascular endothelial growth factor (VEGF) and low-density lipoprotein receptor-related protein 1 (LRP-1) [119]. Newly studied S2R ligands have also showed promising results in beta-amyloid induced neurologic dysfunction [120]. This impact may be related to restoration of calcium homeostasis offered by sigma-2 ligands [121]. Additionally, reductions in neuroinflammation from S1R have offered promising results in models of Alzheimer's Disease [111,112]. Oxidative damage plays a critical role in the development of neurologic impairment [122]. PRE-084 can provide antioxidant properties during times of cell stress, offering safety from toxicity and prolonging neuroprotection through preservation of synaptic connections [123,124].

4.2. Sigma-1 Receptor in Demyelinating Disorders

Demyelinating disorders, both inherited and acquired, have been studied in respect to their response to S1R agonism as well. Krabbe Disease is an autosomal recessive disorder marked by neurodegeneration and resultant demyelination [125]. Treatment with donepezil in models of Krabbe Disease had both preservation of myelin as well as a reduction in reactivity of glial cells, contributing

to neuroprotection [126]. This remains true for other, rare genetic neurodegenerative disorders such as Wolfram Syndrome and Vanishing White Matter Disease (VWM) [127–130]. MS is an acquired and autoimmune disorder that leads to inflammation as well as demyelination and loss of neuronal structures [131]. Studies investigating models of MS concluded that S1R agonists were able to attenuate worsening clinical course, offering a promising avenue for future clinical indications [103,132]. The mechanism of action for protection in MS is thought to be due to protection of oligodendroglia from apoptosis and reactive oxygen species [83].

4.3. *Sigma-1 Receptor in ALS*

ALS is a devastating neurodegenerative disease, with the most common inherited form stemming from a mutation in the C9orf72 gene [133]. S1R is critical to maintaining MAMs, and instability of these domains can predispose to the development of ALS [134,135]. Unregulated autophagy can lead to this critical condition, among other neurodegenerative disorders [136]. A common selective serotonin reuptake inhibitor (SSRI), fluvoxamine, is a S1R agonist that has been shown to restore regulation of autophagy in inherited ALS through stabilization of nucleoporins [137]. Other treatments with agonists such as pridopidine, PRE-084, and SA4503 led to improvement of motor behavior and neuroprotection in mouse models of ALS [138,139]. Interestingly, in the same study, BD1063, an antagonist of S1R, had a similar neuroprotective effect [139]. Another mechanism leading to the development of ALS is the accumulation of RAN proteins within the nervous system [140]. Overexpression of S1R led to less accumulation of RAN, offering a new potential mechanism for treatment [141]. Additionally, a common hallmark in ALS are mutations in the Cu/Zn superoxide dismutase (SOD1) gene, leading to accumulation of neurofilaments. Treatment with pridopidine led to a reduction in this buildup, opening new avenues for treatment of this critical disease [142,143].

4.4. *Sigma-1 Receptor in Huntington's Disease*

Huntington's Disease is an inherited neurodegenerative disorder marked by a progressive loss of neurons through one's lifespan, with resultant debilitating, uncontrolled movements [144]. Like other neurodegenerative disorders, mitochondrial dysfunction is critical to the pathogenesis [145]. In models of HD, pridopidine restored the antioxidant response and decreased levels of reactive oxygen species within the mitochondria [82,146]. Other studies have found that S1R agonism can reduce endoplasmic reticulum stress or restore calcium homeostasis, contributing to attenuation of disease progression [147–150]. Development of new treatment modalities are critical, as there are no disease-modifying medications for HD available currently. Ongoing clinical trials offer promising results and show less decline in patients [151].

4.5. *Sigma-1 Receptor in Parkinson's Disease*

Parkinson's Disease is one of the most common neurodegenerative disorders characterized by a general slowing of movement as well as tremor and rigidity [152]. Toxic accumulation of alpha-synuclein in the nervous system can lead to mitochondrial dysfunction and the degeneration resulting in this pathology [153]. Accumulation of alpha-synuclein can be worsened with S1R deficiencies, showing its importance in preventing this neurodegenerative disorder [154]. Antagonists of S2R potentially attenuate the alpha-synuclein induced neurodegeneration and offer a novel treatment modality [155]. S1R agonists, alone or when combined with nicotinic agonists, have also offered promising protection of the dopaminergic neurons commonly impacted in PD [156,157]. In addition, there are therapeutic strategies emerging using S1R agonism to restore already damaged neurons in PD [158]. Levodopa is a common treatment in PD, however common side effects include dyskinesia [159]. S1R agonists not only offered neuroprotection but were able to decrease levodopa induced dyskinesia [160,161]. S1R antagonists may also play a role in altering the progression of PD. One study found that S1R inhibits the transient receptor potential canonical (TRPC) channel, which is important for calcium regulation and maintaining cell viability. S1R antagonism led to reversal of

this inhibition which resulted in dopaminergic neuroprotection [162]. Other studies show that lower levels of S1R reduce neurotoxicity in dopaminergic cells through suppression of the NMDA receptor (NMDAR) and resulting excitotoxicity [163].

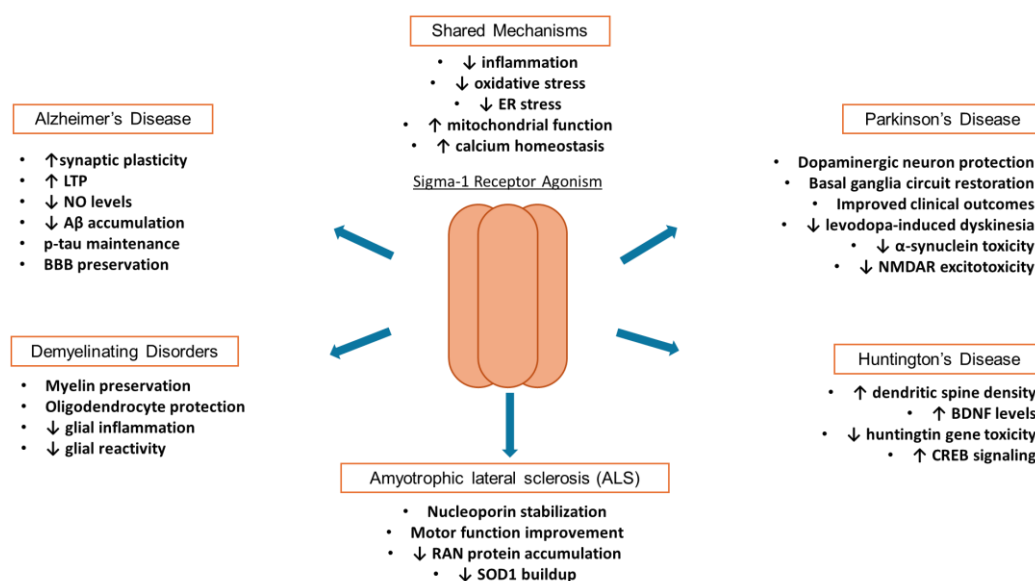


Figure 1. Effects of sigma-1 receptor agonism on neurodegenerative disorders. Agonism of sigma-1 receptor can dampen inflammation and reduce ER and oxidative stresses while promotes mitochondrial functions and calcium homeostasis. .

5. Conclusions

In conclusion, as shown in Figure 1, sigma receptors have emerged as critical modulators of cellular homeostasis and neuroprotection. Their widespread expression has paved the road for extensive research into their pathologic and pharmacologic roles. The sigma receptors represent an intricate pharmacologic target with implications in multiple disease states of the nervous system. Their versatile roles across a variety of pathologies emphasizes their potential as novel therapeutic targets in future research. Contradictory findings in certain pathologies warrant the need for temporal and tissue specific modulation to define the conditions in which sigma receptor activation or inhibition is most beneficial. Combination therapies may soon offer use to provide mitigation for presently incurable diseases.

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