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Sigma receptors as potential therapeutic targets for neuroprotection

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Abstract

Sigma receptors comprise a unique family of proteins that have been implicated in the pathophysiology and treatment of many central nervous system disorders, consistent with their high level of expression in the brain and spinal cord. Mounting evidence indicate that targeting sigma receptors may be particularly beneficial in a number of neurodegenerative conditions including Alzheimer's disease, Parkinson's disease, stroke, methamphetamine neurotoxicity, Huntington's disease, amyotrophic lateral sclerosis, and retinal degeneration. In this perspective, a brief overview is given on sigma receptors, followed by a focus on common mechanisms of neurodegeneration that appear amenable to modulation by sigma receptor ligands to convey neuroprotective effects and/or restorative functions. Within each of the major mechanisms discussed herein, the neuroprotective effects of sigma ligands are summarized, and when known, the specific sigma receptor subtype(s) involved are identified. Together, the literature suggests sigma receptors may provide a novel target for combatting neurodegenerative diseases through both neuronal and glial mechanisms.

Keywords

Glia; Neurodegeneration; Neurotoxicity; Sigma receptors

1. Sigma receptor background

Sigma receptors were first proposed in 1976 based on pharmacological studies, followed by biochemical characterizations during the 1980s (Matsumoto et al., 2007). Today, two subtypes of sigma receptors are recognized, sigma-1 and sigma-2. Both subtypes are highly expressed within the central nervous system (CNS), and they can be distinguished from each other based on differences in their drug selectivity patterns and molecular biological profiles (Matsumoto et al., 2007).

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Sigma-1 receptors are ligand-gated chaperone proteins. They have been cloned with high homology and identity in several species including rodents and humans (Matsumoto et al., 2007). Upon ligand activation, they can translocate to different cellular compartments and have been reported in the endoplasmic reticulum (ER), mitochondria, nuclear membrane, and plasma membrane (Matsumoto et al., 2007). As chaperones, they do not possess their own signaling machinery like G protein coupled receptors (GPCRs), and instead, transduce alterations in cellular function by modulating other cellular targets (Su et al., 2010). In general, deficits in sigma-1 receptors are associated with neurodegeneration, while activation or overexpression of this subtype can convey neuroprotective effects or rescue cells from damage in a number of model systems (Table 1).

Sigma-2 receptors, in contrast, have yet to be cloned and are concentrated in lipid rafts where they can influence calcium signaling through sphingolipid products. Although some reports have suggested that they share identity with the progesterone receptor membrane component 1 (PGRMC1) (Xu et al., 2011), this remains controversial since other more recent data suggest that the two proteins are distinct entities. Activation of sigma-2 proteins nevertheless produces consistent cytotoxicity across a number of model systems, and antagonism or inhibition of their function can mitigate cell death (van Waarde et al., 2010). Most studies involving sigma-2 receptors have, however, utilized tumor models and relatively little is known about the influence of this subtype in the context of the CNS.

2. Modulation of excitotoxicity and oxidative/nitrosative stress

The excess release of glutamate and generation of reactive species when sustained and unmitigated can damage neurons, and have been implicated in a number of neurodegenerative conditions. The effects of sigma ligands on these initiating events are summarized in this section, with almost all of the data to date focusing on the involvement of the sigma-1 subtype.

2.1. Excitotoxicity

A number of pathological states including stroke and traumatic brain injury results in an excessive and sustained release of glutamate, leading to abnormally high influx of calcium into the cell and downstream toxic reactions culminating in cell damage and death, a phenomenon known as excitotoxicity (Sheldon and Robinson, 2007). Among the glutamate receptor subtypes, the N-methyl-D-aspartate (NMDA) receptors appear to play a particularly important role in excitotoxicity. Sigma receptor ligands have displayed neuroprotective effects against excitotoxic mechanisms in retinal ganglion cells, primary neuronal cultures, and ischemic stroke models (DeCoster et al., 1995; Dun et al., 2007; Shen et al., 2008). Of note, the sigma receptor agonist DTG (1,3-di-o-tolylguanidine) has been shown to enhance neuronal survival when administered 24 h after ischemic stroke in rats (Ajmo et al., 2006). The possible mechanisms whereby sigma receptor ligands have the potential to mitigate excitotoxicity include: i) attenuating the release of glutamate (Lobner and Lipton, 1990), ii) reducing the level of activation or expression of NMDA receptors (Zhang et al., 2011), iii) altering intracellular calcium levels (Monnet, 2005), and iv) decreasing reactive species (see below). Both sigma receptor subtypes are likely involved, though the sigma-1 receptor subtype may play a more prominent role. In particular, the sigma-1 receptor subtype has

been implicated in modulating neuronal responses to NMDA receptor stimulation, possibly through direct interaction with specific subunits of the NMDA receptor (Balasuriya et al., 2013) or indirectly through the modulation of other ion channels (Martina et al., 2007).

2.2. Oxidative/nitrosative stress

In addition to glutamate, excessive release of other neurotransmitters including dopamine and serotonin can cause the generation of reactive oxygen species (ROS) through auto-oxidation reactions that form harmful quinones, superoxide radicals, hydroxyl radicals, and hydrogen peroxide. These ROS injure neurons and surrounding cells via oxidative damage to cellular components such as lipids, proteins, and DNA. In addition to ROS, damaging reactive nitrogen species (RNS) can also be generated under pathological conditions in the CNS. Selective sigma antagonists such as AC927 (1-(2-phenylethyl)piperidine) and SN79 (6-acetyl-3-(4-(4-(4-fluorophenyl)piperazin-1-yl)butyl)benzo[d]oxazol-2(3H)-one), have been shown to attenuate the levels of ROS/RNS following toxic exposures to methamphetamine (Kaushal et al., 2012; Kaushal et al., 2014). As the aforementioned antagonists have high affinity for both sigma-1 and sigma-2, further studies are needed to delineate which of the two sigma receptor subtypes can mitigate ROS/RNS production. A large body of literature suggests that sigma-1-mediated attenuation of ROS/RNS levels is associated with agonist, rather than antagonist actions. Consistent with this, knockout of the sigma-1 subtype in mice has shown an increased ROS production (Pal et al., 2012), while the application of sigma-1 agonists reduce ROS/RNS production caused by ischemia, diabetes, and amyloid-beta toxicity (Behensky et al., 2013a; Smith et al., 2008; Yang et al., 2010). The specific mechanisms through which sigma ligands mitigate the harmful effects of ROS/RNS are still being elucidated, but include modulation of nitric oxide synthase (NOS) enzyme activity (Vagnerova et al., 2006; Yang et al., 2010) and intrinsic and extrinsic cell death pathways (Kaushal et al., 2014). Activation of the sigma-1 subtype with agonists such as PRE-084 (2-morpholin-4-ylethyl 1-phenylcyclohexane-1-carboxylate) and (+)-pentazocine can also increase antioxidant proteins through the nuclear factor- κ B (NF- κ B) pathway in an *in vitro* model of Huntington's disease (Hyrskyluoto et al., 2013) and enhance antioxidant genes through activation of antioxidant response elements in COS-7 cells (Pal et al., 2012), further indicating a role for the stimulation of this subtype in mitigating ROS/RNS production.

3. Modulation of mitochondrial death cascades and ER stress

Oxidative/nitrosative stress is capable of triggering a cascade of intracellular signaling events that can be damaging to neurons. The best characterized pathways include mitochondrial death and ER stress pathways. Sigma receptors are located on the ER and mitochondria and are thus positioned within the cell to influence these processes.

3.1. Mitochondrial death pathways

Mitochondrial dysfunction can trigger a host of deleterious effects in cells, including the generation of ROS/RNS, the activation of damaging caspases and other pro-apoptotic factors. The activation of sigma-1 receptors can be targeted to convey neuroprotection by preserving anti-apoptotic genes like *bcl-2* (Meunier and Hayashi, 2010), as has been

reported in a cerebral focal ischemia model (Yang et al., 2007) and mouse neuronal cultures exposed to HIV-1 envelope protein gp120 (Zhang et al., 2012). Sigma-1 receptor agonists can also regulate intracellular calcium levels and prevent the activation of pro-apoptotic genes and caspases in retinal ganglion cells (Tchedre and Yorio, 2008) as well as in rat cortical neurons with prolonged exposure to amyloid-beta peptide (Behensky et al., 2013a).

In tumor cells, sigma-2 receptor agonists elicit a number of caspase-dependent and independent mitochondrial death pathways (Crawford and Bowen, 2002; Garg et al., 2014), suggesting that similar mechanisms may be activated in the CNS although such studies have yet to be conducted. Specifically, sigma-2 receptor agonists have been reported to precipitate caspase-dependent Bid cleavage and the release of apoptosis-promoting factors from the mitochondria (Wang and Bowen, 2006), providing a logical point of intervention for sigma-2 antagonists to promote neuroprotection.

3.2. ER stress pathways

Excesses of unfolded proteins, ROS/RNS and/or disruptions in ER calcium levels can disrupt ER function and induce ER stress signaling through three distinct pathways: activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE-1), and protein kinase R (PKR)-like ER kinase (PERK) (Tabas and Ron, 2011). The induction of these pathways results in gene and protein expression alterations aimed at counteracting the ER stressor, whereas severe or prolonged ER stress can result in apoptosis and cell death (Tabas and Ron, 2011). The sigma-1 receptor is enriched at the mitochondrial-associated ER membrane (MAM), a subdomain of the ER important for cellular survival, and exists in a dormant state in association with BiP/Grp78, a key regulator of ER stress, suggesting that it may play an important role as a chaperone modulating ER stress pathways (Hayashi and Su, 2007). Indeed, overexpression and/or knockdown of sigma-1 receptors has been shown to modulate cellular responses to ER stress *in vitro*, including phosphorylation levels of PERK or IRE-1, and cleavage of ATF6 elicited by the ER stressor thapsigargin in CHO cells (Hayashi and Su, 2007; Mori et al., 2013). The exact mechanism whereby sigma-1 receptors may be altering the activity or levels of these stress proteins remains under investigation, but may involve direct interaction, as in the case with IRE-1 in CHO cells (Mori et al., 2013), and/or indirectly through transcriptional regulation as seen in retinal cells and human lenses (Ha et al., 2014; Wang et al., 2012).

4. Modulation of glial mechanisms that contribute to neurodegeneration

In addition to their presence on neurons, sigma-1 and sigma-2 receptors are also found on glia, and their functional implications in these non-neuronal cells are just beginning to be elucidated. Microglia and astrocytes are of particular interest because they are recognized contributors in a variety of neurodegenerative processes (Perry et al., 2010).

4.1. Microglia

Microglia are the resident macrophages of the CNS that function in maintaining homeostasis by sensing deviations from the normal brain environment which often result in neurodegenerative conditions. Upon activation by perturbations of their surrounding

environment, microglia can undergo transformation to different response phenotypes, which have traditionally been categorized as M1 and M2 microglia (Perry et al., 2010). The classical activation of microglia (M1) is associated with an up regulation of a variety of cell surface proteins, release of pro-inflammatory cytokines, generation of ROS/RNS, and subsequent neuronal damage (Czeh et al., 2011; Perry et al., 2010). In contrast to M1 microglia, which are associated with inflammation and degeneration, M2 microglia are associated with regeneration or anti-inflammatory processes (Czeh et al., 2011). Sigma receptors are found in microglial cells, and the data to date show that sigma ligands produce neuroprotective effects by mitigating the deleterious effects of M1 microglia; there is little to no evidence thus far for the promotion of M2 microglia by sigma ligands to convey neuroprotective effects (Robson et al., 2013).

Sigma receptor ligands modulate several aspects of microglial activation *in vitro* and *in vivo*, including migration and increases in cytokine release or gene expression in response to various activators such as adenosine triphosphate, lipopolysaccharide, amyloid-beta, and methamphetamine (Behensky et al., 2013a; Hall et al., 2009; Robson et al., 2013). The activation of sigma-1 receptors in particular, with agonists such as PRE-084, can protect against microglia reactivity as reported in rodent models of amyotrophic lateral sclerosis (ALS), experimental parkinsonism, and excitotoxic perinatal brain injury (Francardo et al., 2014; Griesmaier et al., 2012; Mancuso et al., 2012). These data indicate that sigma receptor ligands are capable of modulating the functionality of immune cells, including those present within the CNS. An involvement of the sigma-2 subtype is also suggested as many of the ligands studied to date on microglial function interact with both sigma-1 and sigma-2 receptors; however, studies to specifically investigate the role of sigma-2 receptors on microglial function have yet to be conducted.

4.2. Astrocytes

Astrocytes are activated in response to a variety of CNS insults through a process termed astrogliosis, whereby they undergo distinct morphological changes and display an increase in the expression of glial fibrillary acidic protein (Raivich et al., 1999). Many neurotoxicants induce astrogliosis through the activation of JAK2/STAT3 signaling by stimulating gp130-linked cytokine signaling resulting from neuroinflammation (Hebert and O'Callaghan, 2000; Van Wagoner and Benveniste, 1999). The sigma receptor ligand SN79 prevents OSMR β /gp130-induced STAT3 phosphorylation and astrogliosis in the striatum following neurotoxic exposures to methamphetamine (Robson et al., 2014). The specific sigma receptor subtype(s) involved in this effect remain unknown since SN79 interacts with both sigma-1 and sigma-2 receptors. Activation of sigma-1 subtype however appears to be beneficial, as treatment with selective sigma-1 agonist PRE-084 treatment significantly reduced reactive astrogliosis in a rodent model of ALS (Peviani et al., 2014).

5. General conclusions and future perspectives

Sigma receptor ligands affect multiple aspects of neurodegeneration, including varied cellular mechanisms and cell types (Fig. 1), with the two subtypes playing distinct, but potentially synergistic roles. This ability of sigma receptor ligands to modulate neurodegenerative processes across interacting cell types in the CNS suggests the potential

for these drugs to elicit a more coordinated response than that produced through traditional therapeutic targets. While the influence of sigma-1 receptors on neurodegenerative conditions appears well accepted, the role of the sigma-2 subtype remains understudied due to the paucity of experimental tools, and future studies in this area are needed. Noteworthy is the modulatory action of sigma-1 receptor agonists, which might be therapeutically advantageous in clinical practice, exerting efficacies only under pathological conditions while sparing normal physiological activity. For example, the selective sigma-1 receptor agonist PRE-084 improved motor function and restored dopaminergic fibers in a rodent model of experimental parkinsonism but had no effects in the sham-lesioned cohort (Francardo et al., 2014). Although additional studies to further delineate specific cellular mechanisms are still needed, the data to date suggests sigma receptors are very promising targets for developing new drugs to treat and understand neurodegeneration. In addition, future studies involving clinical populations will be critical for validating the neuroprotective potential of sigma receptor ligands against a myriad of neurodegenerative conditions.

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Fig. 1.

Hypothesized mechanisms through which sigma (σ) receptors elicit neuroprotective and/or neurorestorative effects. Injury and/or inflammation in the CNS may stimulate an excessive and sustained glutamate release, which leads to abnormal increases in intracellular calcium levels and the generation of ROS/RNS. Subsequently, a disruption of the Bcl-2 family of proteins and activation of mitochondrial death cascade pathways and ER stress can contribute to cell damage and/or death. Moreover, the activation of microglia and astrocytes in response to injury and/or inflammation can amplify neuronal processes that contribute to neurotoxicity. σ Receptors can intervene at a number of points in this process, including attenuating glutamate release and NMDA receptor activity, mitochondria death pathway and ER stress activation, ROS/RNS production and reactive gliosis while promoting the expression of anti-apoptotic factors (e.g., bcl-2) and calcium homeostasis. ER; endoplasmic reticulum; ROS, reactive oxygen species; RNS, reactive nitrogen species; NOS, nitric oxygen synthase; NMDA, N-methyl-D-aspartate; GFAP, glial fibrillary acidic protein.

Summary of selected neuroprotective effects of sigma ligands on disease model systems. METH, methamphetamine. MCAO, middle cerebral artery occlusion. PPBP, 4-phenyl-1-(4-phenylbutyl) piperidine.

Table 1

Disease	Model	Sigma ligand	Subtype specificity	Major outcome	Reference
Anyotrophic lateral sclerosis	<i>In vivo</i> SOD1 ^{G93A} mouse model	PRE-084	Sigma-1	<ul style="list-style-type: none"> Chronic treatment improves survival, and the function and preservation of spinal motor neurons Modulates NMDA receptor function and reduces microglial reactivity 	(Mancuso et al., 2012)
Alzheimer's disease	<i>In vitro</i> A β ₂₅₋₃₅ -induced toxicity in primary microglia culture	A β 0azole	Nonselective	<ul style="list-style-type: none"> Decreases microglial activation and cell death Reduces expression of Bax and caspase-3 Increases expression of Bcl-2 Blocks increases in intracellular calcium and RNS production 	(Behensky et al., 2013a, b)
Huntington's disease	<i>In vitro</i> PC6-3 cell model transfected with mutant huntingtin proteins	PRE-084	Sigma-1	<ul style="list-style-type: none"> Single treatment before behavioral tests shows anti-amnesic effects in spontaneous alternation performance in the Y-maze and step-through passive avoidance procedure Single pretreatment or chronic post-treatment blocks lipid peroxidation in the hippocampus and learning deficits in the step-through passive avoidance procedure 	(Meunier et al., 2006)
METH neurotoxicity	<i>In vitro</i> Differentiated NG108-15 cell model	SN79	Nonselective	<ul style="list-style-type: none"> Increases cellular antioxidants and reduces ROS/RNS production Counteracts the down regulation of NF-κB pathway and decrease in calpastatin level 	(Hyrskyluoto et al., 2013)
				<ul style="list-style-type: none"> Attenuates ROS/RNS production and activation of caspases Attenuates cell death at normal (37°C) and elevated (40°C) cell culture temperature 	

Disease	Model	Sigma ligand	Subtype specificity	Major outcome	Reference
Parkinson's disease	<i>In vivo</i> Repeated METH dosing mouse model	SN79	Nonselective	• Pretreatment reduces striatal terminal damage and hyperthermia	(Kaushal et al., 2013; Robson et al., 2014)
				• Pretreatment blocks striatal reactive astrogliosis through mitigation of OSMR/gp130 signaling and STAT3 phosphorylation	
				• Post-treatment restores striatal dopamine levels by 25%	
Retinal degeneration	<i>In vivo</i> 6-hydroxydopamine mouse lesion model	PRE-084	Sigma-1	• Chronic treatment improves motor function and density of dopaminergic fibers	(Francardo et al., 2014)
				• Reduces microglial activation and increases neurotrophic factors and the activation of ERK1/2 and Akt	
	<i>In vitro</i> Glutamate-induced cell death in retinal ganglion cells (RGCs)	(+)SKF10047	Sigma-1	• Mitigates intracellular calcium overload and cell death	(Tchedre and Yorio, 2008)
				• Decreases Bax expression and caspase-3 activation	
				• Reduces cell death, cleavage of pro-caspase 12, and induction of BiP and eLF2α in FHL124 cells	
Stroke	<i>In vivo</i> H ₂ O ₂ -induced toxicity in human lens epithelial cells (FHL124) and human whole lenses	(+)Pentazocine	Sigma-1	• Reduces cell death, LDH release and opacification in whole lenses	(Wang et al., 2012)
				• Chronic treatment at onset of diabetes preserves retinal architecture and maintains uniform organization of radial Müller fibers	
	<i>In vivo</i> <i>Ins2^{Mtd/+}</i> mouse model of spontaneous arising diabetic retinopathy	(+)Pentazocine	Sigma-1	• Reduces cell death and ROS/RNS generation	(Smith et al., 2008)
				• Blocks intracellular Ca ²⁺ overload induced by sodium azide and glucose deprivation	
				• Treatment 24h post-MCAO decreases infarct size, neurodegeneration and inflammation	

Disease	Model	Sigma ligand	Subtype specificity	Major outcome	Reference
	Mouse stroke model; Transient MCAO	(+)-Pentazocine	Sigma-1	<ul style="list-style-type: none"> Treatment before reperfusion reduces infarct size through inhibition of inducible NOS 	(Vagnerova et al., 2006)
	Piglet model of neonatal hypoxic-ischemia	PPBP	Nonselective	<ul style="list-style-type: none"> Treatment post resuscitation reduces striatal neuronal damage and ROS/RNS stress Modulates neuronal NOS/ postsynaptic density-95 coupling 	(Yang et al., 2010)