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Perspective

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.

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).

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

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Table 1
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.

Disease	Model	Sigma ligand	Subtype specificity	Major outcome	Reference
Amyotrophic lateral sclerosis	*In vivo* $SOD1^{G93A}$ mouse model	PRE-084	Sigma-1	• 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	*In vitro* $A\beta_{25-35}$-induced toxicity in primary microglia culture	Afobazole	Nonselective	• 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)
	In vivo $A\beta_{25-35}$-induced toxicity mouse model	PRE-084, Donepezil	Sigma-1	• 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)
Huntington's disease	*In vitro* PC6–3 cell model transfected with mutant huntingtin proteins	PRE-084	Sigma-1	• Increases cellular antioxidants and reduces ROS/RNS production • Counteracts the downregulation of NF-κB pathway and decrease in calpastatin level	(Hyrskyluoto et al., 2013)
METH neurotoxicity	*In vitro* Differentiated NG108–15 cell model	SN79	Nonselective	• Attenuates ROS/RNS production and activation of caspases • Attenuates cell death at normal (37 °C) and elevated (40 °C) cell culture temperature	(Kaushal et al., 2014)
	In vivo Repeated METH dosing mouse model	SN79	Nonselective	• Pretreatment reduces striatal terminal damage and hyperthermia • Pretreatment blocks striatal reactive astrogliosis through mitigation of OSMR/gp130 signaling and STAT3 phosphorylation • Post-treatment restores striatal dopamine levels by 25%	(Kaushal et al., 2013; Robson et al., 2014)
Parkinson's disease	*In vivo* 6-hydroxydopamine mouse lesion model	PRE-084	Sigma-1	• Chronic treatment improves motor function and density of dopaminergic fibers • Reduces microglial activation and increases neurotropic factors and the activation of ERK1/2 and Akt	(Francardo et al., 2014)
Retinal degeneration	*In vitro* Glutamate-induced cell death in retinal ganglion cells (RGCs)	(+)-SKF10047	Sigma-1	• Mitigates intracellular calcium overload and cell death • Decreases Bax expression and caspase-3 activation	(Tchedre and Yorio, 2008)
	H_2O_2-induced toxicity in human lens epithelial cells (FHL124) and human whole lenses	(+)-Pentazocine	Sigma-1	• Reduces cell death, cleavage of pro-caspase 12, and induction of BiP and eLF2α in FHL124 cells • Reduces cell death, LDH release and opacification in whole lenses	(Wang et al., 2012)
	In vivo $Ins2^{Akita/+}$ mouse model of spontaneous arising diabetic retinopathy	(+)-Pentazocine	Sigma-1	• Chronic treatment at onset of diabetes preserves retinal architecture and maintains uniform organization of radial Müller fibers • Reduces cell death and ROS/RNS generation	(Smith et al., 2008)
Stroke	*In vitro* Ischemic model of primary rat cortical neurons	DTG Carbetapentane, PRE-084, (+)-Pentazocine	Nonselective Sigma-1	• Blocks intracellular Ca^{2+} overload induced by sodium azide and glucose deprivation	(Katnik et al., 2006)