10 Sigma-1 Receptors and Neurodegenerative Diseases: Towards a Hypothesis of Sigma-1 Receptors as Amplifiers of Neurodegeneration and Neuroprotection

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Abstract

Sigma-1 receptors are molecular chaperones that may act as pathological mediators and targets for novel therapeutic applications in neurodegenerative diseases. Accumulating evidence indicates that sigma-1 ligands can either directly or indirectly modulate multiple neurodegenerative processes, including excitotoxicity, calcium dysregulation, mitochondrial and endoplasmic reticulum dysfunction, inflammation, and astrogliosis. In addition, sigma-1 ligands may act as disease-modifying agents in the treatment for central nervous system (CNS) diseases by promoting the activity of neurotrophic factors and neural plasticity. Here, we summarize their neuroprotective and neurorestorative effects in different animal models of

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acute brain injury and chronic neurodegenerative diseases, and highlight their potential role in mitigating disease. Notably, current data suggest that sigma-1 receptor dysfunction worsens disease progression, whereas enhancement amplifies pre-existing functional mechanisms of neuroprotection and/or restoration to slow disease progression. Collectively, the data support a model of the sigma-1 receptor as an amplifier of intracellular signaling, and suggest future clinical applications of sigma-1 ligands as part of multi-therapy approaches to treat neurodegenerative diseases.

Keywords
Neurorestoration • Stroke • Parkinson's disease • Alzheimer's disease • Amyotrophic lateral sclerosis

10.1 Introduction

Neurodegeneration is characterized by the loss of neuronal integrity, in both structure and function, and can result from acute injury or chronic disease progression. Neurodegenerative diseases are a major cause of morbidity and mortality among the aging population worldwide. The World Alzheimer Report, for example, estimates 46.8 million people worldwide are living with dementia as of 2015 [1]. Based on current trends, this number is projected to almost double about every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050 [1, 2], making efforts to understand and treat these conditions crucial to maintaining the health of an increasingly large demographic. While current treatments for neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and stroke can temporarily alleviate some symptoms and improve quality of life, they are generally ineffective at slowing or stopping disease progression.

Sigma receptors are increasingly recognized targets for novel therapeutic intervention in neurodegenerative conditions [3]. These proteins are implicated in diverse neural mechanisms, including the modulation of cell survival and function, calcium signaling, neurotransmitter release, inflammation, and synaptogenesis [4–6]. The two established subtypes of sigma receptors, sigma-1 and sigma-2, are highly expressed in the central nervous system (CNS), and are distinguishable pharmacologically, functionally, and by molecular size [7].

The present chapter focuses on putative neuroprotective roles conferred by sigma-1 receptor activity as this receptor is the better characterized of the two subtypes. If both subtypes may be involved in an effect described here, we refer to sigma receptors in general, rather than specifying the subtype. We begin with a brief overview of the neuroprotective and restorative effects of sigma-1 ligands in various animal models of neurodegenerative diseases. "Neuroprotection" and "neurorestoration" are terms that can be interpreted in a variety of ways. In the context of this review, neuroprotection is any sequence of events that interrupts or slows the sequence of injurious biochemical and molecular events that, if left unchecked, would likely lead to cell damage and/or loss. Neurorestoration is the regeneration of functional tissue, which is impacted by the capacity of surviving cells to adapt after injury and of new cells (through neurogenesis and/or recruitment of glial cells to damaged areas) to support repair. This is followed by a summary of how sigma-1 ligands may confer their therapeutic effects by modulating mechanisms that are common across a wide array of neurodegenerative conditions, including excitotoxicity, Ca^{+2} dysregulation, mitochondrial and endoplasmic reticulum (ER) dysfunction, neuroinflammation, and

reactive gliosis. In addition, sigma-1 ligands may promote neurorestorative processes to enhance the structure and function of neurons that become compromised in disease, or to stimulate the influx of new cells to assist in repairing damage to the nervous system. Finally, we discuss the model of the sigma-1 receptor as an "amplifier" of intracellular signaling, the resulting ways that sigma-1 receptors may be involved in disease and therefore exploited therapeutically, and the potential application of sigma-1 ligands as part of combined therapeutic approaches in future clinical studies of neurodegenerative diseases.

10.2 Sigma-1 Receptor Ligands in Animal Models of Neurodegenerative Diseases

In general, in model systems of neurodegenerative diseases, deficits in sigma-1 receptor level or activity are associated with neurodegeneration, while sigma-1 receptor activation or overexpression are associated with neuroprotection. Consistent with this, most reports of beneficial effect come from studies of sigma-1 agonists, with these effects generally showing sensitivity to sigma-1 antagonism. Below, we highlight the neuroprotective effects of sigma-1 receptors in several animal models of neurodegenerative disease. In our recent review, we highlight additional models where targeting sigma-1 receptors alters neurodegenerative disease processes [3].

10.2.1 Stroke

Acute brain injury following cerebral ischemia (stroke) and trauma can lead to long-term neurological and psychiatric deficits. As the primary insult (e.g., direct mechanical damage) cannot be therapeutically influenced, the goal of treatment is to limit secondary injury processes. Following cerebral ischemia, both necrotic and apoptotic cell death can be induced through complex interactions of pathological processes, including excitotoxicity and inflammation [8,9]. Neuroprotective and neurorestorative effects of sigma-1 agonists (e.g., decreasing cell death, protecting against tissue damage, and increasing synaptic protein expression) have been shown in multiple animal models of stroke, including mouse [10], rat [11–16], gerbil [17] and cat [18]. In rat models of stroke, for example, decreased infarct volume as well as enhanced neuronal survival were observed following acute treatment with a sigma agonist 24 h after the onset of ischemia [14, 15]. In addition, functional recovery with or without changes in infarct volume was observed when sigma agonists were administered as late as 2 days post-stroke [15, 19]. The potential to treat at extended times following the initial embolic injury warrants further investigation, as the only available post-stroke treatment approved for use in humans is thrombolytics, which is limited to 4 h post-stroke due to the risk of hemorrhagic transformation (i.e., conversion of an ischemic stroke to a hemorrhagic one following reperfusion) [20]. Of note, Ruscher and colleagues demonstrated that treatment of rats subjected to permanent or transient middle cerebral artery occlusion (MCAO) with the selective sigma-1 agonist SA4503 (1-[2-(3,4-dimethoxyphenyl) ethyl]-4-(3-phenylpropyl) piperazine) starting 2 days after injury conferred significantly better recovery rates of sensorimotor function compared with the vehicle group [19]. The significant improvement of neurological function following MCAO was associated with increased levels of the synaptic proteins neurabin and neurexin in the peri-infarct area [19]. This improvement was sustained 2 weeks after discontinuation of SA4503 [19]. These results suggest that stimulation of sigma-1 receptors promote neural adaptations (e.g., increases in synaptic proteins and potentially synaptic connections) to facilitate recovery following MCAO [19].

10.2.2 Other Acute CNS Injury

Additional beneficial effects of sigma agonists have been reported in other models of acute

CNS injury. Following spinal root avulsion in adult rats, administration of the sigma-1 agonist PRE084 (2-(4-morpholinethyl)1-phenylcyclohexanecarboxylate) promoted motor neuron survival [21]. Co-administration of the sigma-1 antagonist BD1063 (1-[2-(3,4-dichlorophenyl) ethyl]-4-methylpiperazine) blocked this effect [21]. In another study, the sigma agonist PPBP (4-phenyl-1-(4-phenylbutyl) piperidine) improved neurological function and reduced striatal cell death when administered after global hypoxia-ischemia (induced by asphyxic cardiac arrest followed by resuscitation) in newborn piglets [22]. An additional study showed that the sigma-1 agonist PRE084 reduced cortical lesion size and cell death following excitotoxic perinatal brain injury in newborn mice [23]. However, confirmation of a sigma-1-mediated mechanism using an antagonist was not tested in the two aforementioned studies involving neonates.

10.2.3 Amyotrophic Lateral Sclerosis

In a superoxide dismutase 1 (SOD1)-G93A mouse model of amyotrophic lateral sclerosis (ALS), daily administration of the selective sigma-1 agonist PRE084 from 8 to 16 weeks of age improved spinal motor neuron function and survival, demonstrated by the preservation of neuromuscular connections and motor neuron number in the spinal cord, maintenance of muscle action potential amplitudes, and improvement in locomotor performance [24]. This attenuation of the disease state was associated with an increase in survival time in PRE084-treated mice compared to controls [24]. In contrast, genetic ablation of sigma-1 receptors accelerated the appearance of motor deficits as well as decreased longevity in the SOD1-G93A mouse model [25].

Sigma-1 agonists may also be effective in cases of SOD-1-independent mechanisms of ALS. Chronic treatment with PRE084 improved motor neuron survival and locomotor performance in the wobbler mouse, which is a model of motor neuron degeneration [26].

10.2.4 Parkinson's Disease

In an intrastriatal 6-hydroxydopamine (6-OHDA) lesion model of Parkinson's disease (PD), mice were treated daily with PRE084 for 5 weeks, starting on the same day as the lesion induction [27]. PRE084 gradually and significantly improved spontaneous forelimb use, along with a partial recovery of dopamine levels and increased dopaminergic fiber densities, compared to saline-treated animals [27]. PRE084 treatment also upregulated neurotrophic factor protein levels and increased activation of their downstream effector pathways [27], further suggesting that sigma-1 receptor activation contributes to the restoration of synaptic connectivity and functional recovery in neurodegeneration disease models.

10.2.5 Alzheimer's Disease

In an amyloid beta (25–35) peptide-induced mouse model of Alzheimer's disease (AD), selective and non-selective sigma-1 agonists improved both molecular and behavioral markers of neurodegeneration [2, 28, 29]. The selective sigma-1 agonist PRE084 and the non-selective sigma-1 agonists donepezil or AVANEX2–73 mitigated spatial working memory deficits in spontaneous alternation tests [2, 28]. They also attenuated contextual long-term memory in the step-through passive avoidance procedure [2, 28]. These effects were mediated, at least in part, by sigma-1 receptors, demonstrated by their sensitivity to the sigma-1 antagonist BD1047 (N-[2-(3, 4-dichlorophenyl) ethyl]-N-methyl-2-(dimethylamino) ethylamine) [2, 28]. In addition, treatment with these sigma-1 agonists decreased amyloid beta-induced lipid peroxidation in the hippocampus, consistent with a role in decreasing oxidative damage; these protective effects were also attenuated by BD1047 [2, 28]. In amyloid beta (25–35)-treated mice exhibiting cognitive deficits, PRE084 or igmesine, another selective sigma-1 agonist, showed greater antidepressant efficacy compared to non-amyloid beta-treated animals [6]. This enhanced efficacy was

not seen with the classic antidepressants desipramine or fluoxetine, suggesting that selective sigma-1 receptor agonists are promising alternatives for alleviating the depressive symptoms in AD patients.

10.2.6 Possible Therapeutic Effects of Sigma-1 Antagonism

There are a few studies that suggest a potential benefit of sigma-1 antagonism to promote neuroprotection, though the specific effects of sigma-1 suppression are unclear. The putative sigma-1 antagonist haloperidol, for instance, reduced infarct volume in a rat model of MCAO [30]. When compared to eight other butyrophenone compounds in an *in vitro* assay of glutamate-induced oxidative stress, the authors found a significant positive correlation between haloperidol's protective potency (i.e., nanomolar vs. micromolar concentration required to increase cell survival) and affinity for sigma-1 receptors [30]; however, haloperidol also has similar nanomolar affinity to other targets, including dopamine, serotonin (5-HT), and alpha adrenergic receptors, making it difficult to attribute its primary effect to sigma-1 antagonism in these models. More selective sigma antagonists have been shown to reduce methamphetamine (METH)-induced neurotoxicity [31] and alleviate neuropathic pain [32]. In wildtype mice, knockout of sigma-1 receptors prevented subchronic administration of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) from causing the motor and histochemical deficits characteristic of PD [33]. This protective effect, however, was not observed in sigma-1 knockout mice [33], suggesting the importance of these receptors in the etiology of the disease. While these and other studies leave open the possibility that sigma-1 antagonism may be beneficial in certain conditions, there is much stronger and more direct evidence that sigma-1 activation is neuroprotective, and therefore that sigma-1 agonist-based therapeutics are more likely to protect against neurodegeneration than antagonists.

10.3 Sigma-1 Receptor Mediated Mechanisms of Neuroprotection

While neurodegenerative diseases are a heterogeneous group of illnesses with distinct clinical phenotypes and diverse etiologies, emerging evidence suggests that they share important pathogenic mechanisms, including excitotoxicity [20, 34, 35], Ca^{2+} dysregulation [36, 37], mitochondrial and ER dysfunction [38–41], inflammation [42, 43], and in some cases, astrogliosis [44]. In addition, neurotrophic factors and neural plasticity have been found to be important targets for disease-modifying treatments for CNS diseases [45–48]. In this section, we focus on the ways in which sigma-1 receptor activity may modulate these mechanisms to elicit neuroprotection.

10.3.1 Glutamate Excitotoxicity

Excitotoxicity occurs when high levels of glutamate cause persistent activation of N-methyl-D-aspartate (NMDA) receptors, allowing an influx of Ca^{2+} that can activate downstream mechanisms of programmed cell death, including the activation of calpains, proteases, protein kinases, nitric oxide synthase (NOS) and the mitochondrial permeability transition pore [34, 49]. Excitotoxicity has been observed in multiple neurodegenerative disease states, including ALS, AD, PD, stroke and METH toxicity [20, 26, 35, 50, 51]. Through the modulation of glutamate and its receptors, sigma ligands have been reported to be neuroprotective against excitotoxicity in retinal ganglion cells (RGCs), primary neuronal cultures, and ischemic stroke models [23, 52–57].

The mechanisms by which sigma ligands modulate excitotoxic glutamate release are poorly understood. However, studies to date implicate multiple mechanisms. In a chronic restraint stress model of depression, for example, stimulation of sigma-1 receptors enhanced glutamate release by increasing presynaptic cytoplasmic release of Ca^{2+} from ER stores [58]. Sigma-1 agonists also inhibited the release of glutamate

evoked by a K^+ channel blocker in cortical nerve endings, in a sigma-1 antagonist-sensitive manner [59]. In addition, treatment with sigma-1 agonists has led to decreased Ca^{2+} entry through presynaptic voltage-dependent Ca^{2+} channels and the suppression of protein kinase C (PKC) signaling cascades, resulting in decreased glutamate release from nerve terminals in the rat cerebral cortex [59].

In addition to influencing glutamate release, sigma-1 receptor activity is implicated in the neuronal responses to NMDA receptor stimulation, both directly, through interactions with specific subunits of the NMDA receptor [60, 61] and indirectly, through the modulation of other ion channels [62]. Sigma-1 receptors have been shown to bind to the cytosolic C-terminal region of the NMDA receptor NR1 subunit in recombinant cells, which can be inhibited by sigma-1 antagonists [63]. Activation of sigma-1 receptors can also increase the interaction between sigma-1 receptors and NR2 subunits of NMDA receptors. This happens concurrently with increased translocation to the cell surface and results in an increase in NMDA receptor availability at the plasma membrane [64]. The authors hypothesized that the relationship between sigma-1 receptors and NR2 subunits is therefore an indirect one, involving direct interactions between sigma-1 receptors and NR1 subunits that are part of the same tetrameric NMDA receptor complex as the NR2 subunits being probed [64]. In another study, activation of sigma-1 receptors induced phosphorylation of NR1 subunits and subsequent potentiation of NMDA receptor function in spinal neurons by modulating PKC signaling via the alpha and epsilon isoforms of PKC [65].

Sigma-1 receptor activation can also affect the interaction of other proteins with NMDA receptors to elicit neuroprotective effects. For example, sigma-1 agonists enhanced the interaction of histidine triad nucleotide binding protein 1 (HINT1) with G-protein coupled receptors (GPCRs) and in turn stimulated GPCR-NMDA interactions, promoting protective effects against excitotoxicity [66]. Downstream of influencing NMDA receptor function and/or activity, sigma-1 agonists have been shown to be neuroprotective by increasing brain-derived neurotrophic factor (BDNF) levels in an ischemia/reperfusion vascular dementia model [67]. This appeared to be mediated through NR2A-CAMKIV (calcium/calmodulin-dependent protein kinase type IV)-TORC1 (transducer of regulated cyclic adenosine monophosphate (cAMP) responsive element-binding protein (CREB) activity) pathways [67].

In addition to NMDA receptors, sigma receptors may regulate (directly or indirectly) other glutamatergic targets including kainate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) glutamate receptors to confer neuroprotective effects. For example, sigma-1 agonists attenuated kainate receptor-induced hippocampal neurotoxicity and seizures by acting downstream and decreasing c-fos/c-jun expression and activator protein (AP)-1 DNA-binding activity [68, 69]. Sigma-1 agonism also afforded neuroprotection by reducing the expression of AMPA receptors in cultured cortical neurons, possibly via decreasing activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling [70], a critical pathway for the maintenance of ionotropic glutamate receptors [71].

10.3.2 Ca^{2+} Dysregulation

High and persistent Ca^{2+} release may contribute to neurotoxicity and cell death. In addition to Ca^{2+} flux through NMDA receptors, there are several additional means by which Ca^{2+} levels can be increased to toxic levels in neurons, including exit from intracellular ER and mitochondria stores, influx through voltage-dependent plasma membrane Ca^{2+} channels, Na^{2+}/ Ca^{2+} exchangers, and acid-sensing ion channels (ASICs) [49].

Sigma-1 agonists have been shown to regulate intracellular Ca^{2+} levels and prevent the increased expression of pro-apoptotic genes and caspases in RGCs [72], as well as in rat cortical neurons with prolonged exposure to amyloid beta peptide [73]. These molecular effects correspond with phenotypic improvements to memory impairments in animal models [29].

In both physiological and pathophysiological conditions, sigma-1 receptors appear to function as chaperones and Ca^{2+} sensors [5, 74–77]. At the ER mitochondrial-associated membrane (MAM), sigma-1 receptors play an important role in regulating Ca^{2+} levels via inositol trisphosphate (IP_3) receptors and maintaining intracellular Ca^{2+} homeostasis [76].

In addition to modulation of intracellular sources of Ca^{2+}, sigma-1 receptors can alter the behavior of plasma membrane ion channels, thereby altering Ca^{2+} uptake into the cell. Sigma-1 agonists have been shown to mediate the elevated intracellular Ca^{2+} levels caused by activation of ASIC-1a during stroke-induced ischemia [78]. Among the Ca^{2+}-associated downstream signaling pathways, sigma-1 agonism reduced the activation of the MAPK/ERK pathway, affording neuroprotection [70]. In rat primary ganglion cells, the sigma-1 agonist (+)-SKF10047 ((2S,6S,11S)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol) inhibited potassium chloride (KCl)-induced Ca^{2+} influx through L-type Ca^{2+} channels, which was reversed by the sigma-1 antagonist, BD1047. This inhibition involved direct interactions between L-type Ca^{2+} channels and sigma-1 receptors [79]. In addition to their effects on neurons, sigma-1 ligands can suppress microglial activation through Ca^{2+}-dependent mechanisms, decreasing the release of inflammatory cytokines [80].

10.3.3 ER Stress

Neurodegenerative conditions associated with ER stress include METH toxicity, HD, AD, ALS and PD [38, 40, 81]. One result of ER dysfunction is the accumulation of unfolded or misfolded proteins within the ER lumen. This accumulation activates the unfolded protein response (UPR), which occurs through three major signaling pathways: protein kinase RNA like ER kinase (PERK), inositol requiring enzyme 1 alpha (IRE1α), and activating transcription factor 6 (ATF6). As chaperones, sigma-1 receptors participate closely in the degradation of unfolded proteins [82], and multiple studies describe sigma-1 receptor modulation of the UPR [76, 83, 84]. Moreover, the C-terminus on the sigma-1 receptor has been shown to interact with the glucose-regulated protein 78 (GRP78)/immunoglobulin heavy-chain binding protein (BiP) [85], a critical regulator of all three arms of the UPR [86]. Following the administration of the Ca^{2+} channel inhibitor thapsigargin or the GPT (UDP-N-acetylglucosamine-dolichol phosphate N-acetylglucosamine-1-phosphate transferase) inhibitor tunicamycin, which are frequently used to model ER stress and induce UPR in cell culture models, sigma-1 receptor expression is upregulated in response to activation of the PERK pathway [87] and more specifically, ATF4, a downstream target of PERK signaling [88]. This upregulation of sigma-1 receptor expression found in HEK293 (human embryonic kidney) and Neuro2a (mouse neuroblastoma) cells can repress cell death signals that accompany ER stress [87]. Consistent with this, overexpression of the sigma-1 receptor decreased the activation of PERK and ATF6 and increased cell survival in Chinese hamster ovary (CHO) cells, whereas knockdown of sigma-1 receptors destabilized the conformation of IRE1 and decreased cell survival following administration of thapsigargin [76, 84].

Not surprisingly, treatment with the selective sigma-1 agonist SA4503 mitigated ER stress and reduced cell death in the retina following light-induced damage [89]. Using the selective 5-HT reuptake inhibitor (SSRI) fluvoxamine, a potent sigma-1 agonist that exhibits stronger affinity for sigma-1 receptors than other SSRIs [90], Omi and colleagues also showed that fluvoxamine, via activation of sigma-1 receptors, upregulated sigma-1 receptor expression and inhibited cell death in Neuro2a cells exposed to tunicamycin (which disrupts protein folding and directly induces the UPR) [88]. The specificity of sigma-1 involvement was confirmed with the addition of the sigma-1 antagonist NE100 (N, N-dipropyl-2-[4-methoxy-3-(2-phenylethoxy) phenyl] ethylamine monohydrochloride), which blocked the effects of fluvoxamine [88].

10.3.4 Mitochondrial Ca^{2+} Uptake and Activity

In their quiescent state, sigma-1 receptors are located in the mitochondrial-associated membrane (MAM) in association with the ER chaperone protein BiP, and under these conditions are inactive. Activation by ligand binding or various pathways of ER stress causes the dissociation of sigma-1 receptors from BiP and allow their participation in multiple downstream pathways.

Within the MAM, activated sigma-1 receptors appear to stabilize IP_3 receptors by protecting them from proteasomal degradation [76] and activate them by promoting their dissociation from the ion channel chaperone protein ankyrin B 220 [91]. This promotes Ca^{2+}-induced Ca^{2+} release from the ER through Ca^{2+}-activated IP_3 production, and then Ca^{2+} trafficking into the mitochondria. Ca^{2+} uptake into the mitochondrial matrix is a sensitive regulator of oxidative phosphorylation. Sub-micromolar increases in matrix Ca^{2+} directly activate multiple enzymes, including glycerol phosphate dehydrogenase, isocitrate dehydrogenase, and oxoglutarate dehydrogenase, and, indirectly (via dephosphorylation) pyruvate dehydrogenase, resulting in increased flux through the Krebs cycle and facilitating increased rates of oxidative phosphorylation. In this way, Ca^{2+} acts as an interorganellar signal to "tune" ATP supply according to the ATP demand dictated by the rest of the cell.

The sigma-1 receptor-IP_3 receptor interaction may promote mitochondrial Ca^{2+} uptake and, ultimately, cell survival [76]. Consistent with this, Shioda and colleagues identified a truncated splice variant of the sigma-1 receptor (short form sigma-1 or sigma-1S) in the mouse hippocampus that localizes to the MAM and complexes with non-truncated sigma-1 receptors, but does not complex with IP_3 receptors [92]. In Neuro2a C3100 cells, exogenous overexpression of non-truncated sigma-1 receptors enhanced ATP- or IP_3-induced mitochondrial Ca^{2+} uptake whereas overexpression of sigma-1S decreased mitochondrial Ca^{2+} uptake compared to control cells [92]. Following tunicamycin-induced ER stress, the exogenous overexpression of non-truncated sigma-1 receptors protected IP_3 receptor proteins from degradation and enhanced ATP production, promoting cell survival [92]. In contrast, overexpression of sigma-1S enhanced IP_3 receptor degradation and decreased mitochondrial Ca^{2+} uptake, resulting in increased apoptosis [92]. These findings suggest that sigma-1S destabilizes IP_3 receptors and diminishes IP_3 receptor-driven mitochondrial Ca^{2+} uptake through the loss of sigma-1-IP_3 receptor interactions, resulting in impaired ATP production and increased apoptosis [92]. Of note, mutations of sigma-1 receptors have been found in neurodegenerative conditions such as ALS [93, 94]. It will therefore be important to further evaluate how truncated sigma-1 receptors may interfere with normal receptor function to affect mitochondrial stability.

There is also experimental support for sigma-1 receptor-mediated maintenance of bioenergetic homeostasis. Though the effects are likely indirect, sigma-1 receptor activation is reported to preserve bioenergetic function in multiple models, supporting a neuroprotective role. The sigma agonist PPBP appears to stabilize mitochondrial membrane potential in neurons undergoing excitotoxic stress through glutamate exposure. This stabilization was associated with decreased neuronal death [95]. Another agonist, BHDP (*N*-benzyl-*N*-(2-hydroxy-3,4-dimethoxybenzyl)-piperazine), appeared to have "mitochondrial protective" effects in a liver model of ischemia/reperfusion [96].

10.3.5 Neuroinflammation

The primary mediators of neuroinflammation in the CNS are microglia, which are macrophage-derived cells residing in the CNS. Although multiple microglial phenotypes are believed to result from CNS insult, they are typically classified as M1 and/or M2 responses, similar to peripheral macrophages [42]. M1 microglia are traditionally considered pro-inflammatory and tend to be associated with damage to the CNS, while M2 microglia are anti-inflammatory and associated with neuronal repair and regrowth [42, 97]. Sigma-1 receptors, expressed in microglial and

neurons, may modulate microglial activation and dampen neuroinflammation. Indeed, many studies have shown that sigma agonists may affect M1 and/or M2 responses, with most studies to date focusing on the M1 response. For example, Robson and colleagues demonstrated that neurotoxic dosing with METH preferably activated M1 microglia responses within the mouse striatum as represented by significant increases in the pan-macrophage markers, cluster of differentiation 68 (CD68) and ionized calcium binding adapter molecule 1 (IBA-1), without concurrent increases in an M2 marker, CD163 [98]. Pretreatment with the sigma ligand SN79 (6-acetyl-3-(4-(4-(4-fluorophenyl) piperazin-1-yl) butyl) benzo[d] oxazol-2(3H)-one) attenuated the increase in CD68 and IBA-1, indicating prevention of METH-induced M1 microglial activation [98]. Associated with this reduction in M1 microglia was an obviation of IL-6 and oncostatin M, showing protection against neuroinflammation [98]. In lipopolysaccharide (LPS)-stimulated murine microglial BV2 cells, the sigma-1 agonist SKF83959 (6-chloro-2,3,4,5-tetrahydro-3-methyl-1-(3-methylphenyl)-1H-3-benzazepine-7,8-diol) prevented M1 microglial activation and decreased pro-inflammatory cytokines, including tumor necrosis factor alpha, IL-1 beta, and inducible NOS [99]. The sigma agonists DTG (1,3-di-(2-tolyl)guanidine) and afobazole have also been shown to suppress microglial activation and migration and the release of inflammatory cytokines in response to not only LPS, but also other microglial activators such as ATP, uridine triphosphate and monocyte chemoattractant protein-1 [100]. In an *in vivo* model of traumatic brain injury, the sigma-1 agonist PRE084 has been shown to reduce IBA-1 expression following controlled cortical impact in association with reduced lesion volume and improved behavior in mice [101]. Similarly, PRE084 also reduced counts of IBA-1 positive microglial cells in a mouse model of ALS [24].

In contrast, in another study in animals with motor neuron disease, treatment with PRE084 increased the number of cells positive for the pan-macrophage marker CD68 and CD206, which is associated with M2 microglial responses [26]. Sigma ligands also improved microglial cell survival during and at least 24 h after ischemia [100], as well as after toxic exposure to amyloid beta in primary microglia cultures [102]. These data suggest that sigma receptors may modify microglial reactivity to strengthen the reparative microglia phenotype (M2) while attenuating the inflammatory response (M1). Further studies should examine both microglial types to better understand the role of sigma-1 receptors on microglia in neurodegeneration and neurorestoration.

Upon disruption of the blood brain barrier by injury, diapedesis of peripheral leukocytes into the brain may also exacerbate neuroinflammation. Sigma-1 receptors are expressed in lymphocytes, and previous studies have shown the ability of sigma-1 ligands to inhibit CD3 lymphocyte proliferation *in vitro* and LPS-induced release of cytokines *in vivo* [103, 104]. Recently, a novel synthetic, high-affinity and selective sigma-1 ligand was examined in a mouse autoimmune encephalitis model [105], which exhibited histopathological changes characterized by peripheral leukocyte infiltration into the brain along with demyelination and axonal loss [106]. The sigma-1 ligand prevented mononuclear cell accumulation and demyelination in the brain and spinal cord while also increasing the proportion of B-cell subsets and regulatory T-cells, resulting in an overall reduction of the clinical signs of experimental autoimmune encephalitis [105]. Sigma-1 receptors may therefore regulate peripheral immune cells to slow the progression of certain CNS diseases.

10.3.6 Reactive Astrogliosis

Reactive astrogliosis is characterized by the "activation" of astrocytes within the CNS, which may result in the proliferation and migration of astrocytes to areas of damage and in some cases, the formation of glial scars. Glial scar formation is hypothesized to protect surrounding neuronal tissue from further damage as a result of excess inflammation. However, the formation of glial scars also can impede repair and thereby inhibit

the ability of neuronal tracts to regenerate [107]. Sigma receptors are found in astrocytes [7], and accumulating data suggests that sigma-1 receptor activity promotes repair following damage to the CNS. For example, following experimental stroke, a 30 % increase of sigma-1 receptor expression was found in astrocytes, and treatment with a sigma-1 agonist enhanced the recovery of sensorimotor function without decreasing infarct size [19]. This led the authors to suggest that the recovery-promoting action of sigma-1 receptors involved astrocytes in the peri-infarct area [19].

In an animal model of PD, sigma-1 receptor distribution was also noted in astrocytes, in addition to neurons. In the striatum, sigma-1 immunoreactivity predominated in astrocytes (vs. neurons), while in the substantia nigra, sigma-1 immunoreactivity was predominant in dopaminergic neurons (vs. astrocytes) [27]. Following 5 weeks of treatment with the sigma-1 agonist PRE084, there was a shift in distribution of sigma-1 receptors from the neuronal and astrocytic cell bodies into the processes [27]. This occurred in association with functional motor recovery. Consequently, sigma-1 agonists may be increasing astrocytic neuroprotective activity by promoting the intracellular trafficking of sigma-1 receptor proteins and potential transport of other protein partners involved in neuroprotective mechanisms to distal regions of astrocytes.

As well as increasing astrocytic activity, sigma ligands have also been shown to reduce astrocytic activity in some studies. Ajmo and colleagues showed that the sigma agonist DTG reduced astrocyte activation 24 h post-stroke [14]. Penas and colleagues also found that the selective sigma-1 agonist PRE084 reduced astrogliosis and ER stress following spinal root avulsion [108]. PRE084 similarly provided neuroprotection and reduced astrogliosis in preclinical ALS [26] and PD models [27]. Furthermore, in an animal model of METH-induced neurotoxicity, METH increased astrogliosis in the damaged striatum, an effect that could be mitigated with a novel sigma ligand; these effects involved modulation of the OSMR-STAT3 signaling pathway [109], which has been implicated in other neurotoxic conditions such as ischemic stroke or peripheral LPS injections [110].

The ability of sigma ligands to modulate the function of astrocytes, in addition to neurons and microglia, suggest that these ligands may be able to facilitate a coordinated response across cell types to achieve therapeutic outcomes. Additional studies to delineate the interplay between these cell types in the nervous system in health and disease are warranted.

10.4 Sigma-1 Receptor-Mediated Mechanisms of Neurorestoration

In addition to targeting sigma-1 receptors to mitigate neurodegenerative processes, accumulating evidence reveals the potential for sigma-1 agonists to stimulate neurorestorative processes after the CNS has been damaged. This can be achieved either by improving the structural and/or functional integrity of existing cells that have become compromised by disease, or by stimulating the incorporation of new cells into the damaged region to support repair. For example, in a mouse 6-OHDA lesion model of PD, treatment with the sigma-1 agonist PRE084 for 5 weeks after lesion induction can rescue animals from both histological and functional deficits that are normally associated with the lesions [27]. The involvement of sigma-1 receptors in the neurorestorative effects has been confirmed by the inability of PRE084 to evoke similar rescue in sigma-1 receptor knockout mice [27]. Specific neurorestorative mechanisms that can be targeted by sigma ligands are only just beginning to be investigated, and those that have been identified are summarized below.

10.4.1 Increased Growth Factor Expression or Activity

Neurotrophins and growth factors play an integral role in nervous system development, maintenance, and plasticity [111]. Aberrant levels of multiple neurotrophins and growth factors have

been implicated in CNS disorders, including neurodegenerative conditions [112]. These proteins have also been proposed as targets for future therapies [113].

Glia-derived neurotrophic factor (GDNF) has long been known to be capable of rescuing neurons following CNS insult [114, 115]. Converging lines of evidence now indicate that sigma-1 receptor activation may stimulate these GDNF-dependent repair mechanisms. In a spinal root avulsion model, daily administration of the sigma-1 agonist PRE084 after axotomization of motor neurons increased motor neuron survival at day 21 post-operation [108]. This recovery was accompanied by an early increase in GDNF expression in astrocytes in the ventral horn day 3 post-operation [108], suggesting that the activation of sigma-1 receptors in glial cells led to the release of survival-promoting trophic factors. The restorative effects to behavior and histology associated with subchronic treatment of PRE084 in the mouse model of PD described above was also accompanied by an upregulation of striatal GDNF and BDNF; GDNF was additionally upregulated in the substantia nigra [27]. Since phosphorylated ERK1/2 and protein kinase B were also increased under these conditions, the data suggest that downstream signaling pathways associated with these trophic factors were activated by PRE084 to promote recovery [27].

In addition, in a mouse model of ALS, subchronic treatment with PRE084 upon symptom onset increased BDNF immunoreactivity in the affected area: the ventral horn of the spinal cord in neurons and notably also in non-neuronal cells [26]. Confirmation that the upregulation of BDNF was mediated through sigma-1 receptors via pharmacological antagonism or genetic manipulation (knockdown or knockout) has yet to be conducted in the ALS model and represents an important future study.

In vitro findings further support a role for sigma-1 receptor activity in regulating BDNF. Heat-induced aggregation of BDNF and GDNF were blocked by purified sigma-1 polypeptides [116]. In addition, the sigma-1 agonist SA4503 stimulated mature BDNF secretion from SH-SY5Y (human neuroblastoma) and B104 (rat neuroblastoma) cells, an effect that could be prevented with the sigma-1 antagonist NE100 [114]. Knockdown of sigma-1 receptors in B104 cells also decreased the ability of the cells to secrete mature BDNF, further underscoring a potential role for sigma-1 receptors in regulating BDNF processing and release [116].

Although not studied in neurodegeneration models, sigma-1 agonists have also been reported to stimulate nerve growth factor (NGF)-induced neurite outgrowth in cultured cells [117–121] and potentiate epidermal growth factor (EGF)-induced neuritogenesis in PC12 (rat pheochromocytoma) cells overexpressing sigma-1 receptors [122]. In addition, sigma-1 activation with PRE084 enhanced neurite outgrowth in cerebellar granule cells via tropomyosin receptor kinase B (TrkB) signaling [123]. These observations raise the possibility that sigma-1 receptor activation has the potential to stimulate the activity of an array of neurotrophic factors to assist in recovery from CNS injury and disease.

10.4.2 Alterations in Neuronal Morphology

In many neurodegenerative conditions, aberrant neuronal morphology is observed. Dendritic and axonal deficiencies, in particular, are expected to compromise the integrity of neuronal connectivity within the CNS [124]. It is therefore noteworthy that sigma-1 receptors are found in key locations within neurons such as the growth cones [125], and agonists can promote neurite outgrowth from these sites through interactions with neurotrophic signaling pathways, as mentioned above. Additional studies have reported that decreased sigma-1 receptor expression can adversely affect dendritic arborization and axonal elongation in *in vitro* systems.

In hippocampal neurons, knockdown of sigma-1 receptors decreased dendritic arborization, diminished the formation and maturation of dendritic spines, and reduced protein markers of functional synapses [126]. Active forms of GTP (guanosine triphosphate)-binding Rac1 (ras-related C3 botulinum toxin substrate 1) and

intact TIAM1 (T-cell lymphoma invasion and metastasis-inducing protein 1) in raft fractions were also reduced in sigma-1 receptor knockdown neurons [126], suggesting the contribution of this signaling pathway to the decreased dendritic arborization. The ability of a constitutively active Rac or caspase-3-resistant TIAM1 construct to rescue spine formation in sigma-1 knockdown neurons was supportive of such a role [126]. In addition, a free radical scavenger (N-acetylcysteine), superoxide dismutase activator (Tempol), or NOS inhibitor (nitro-L-arginine) was able to restore spine formation in sigma-1 receptor knockdown neurons [126]. Together, the data suggest that deficits in sigma-1 receptors can compromise dendritic spine formation and arborization through a free radical-sensitive mechanism involving the Rac1-GTP pathway [126].

Another study recently demonstrated that sigma-1 receptor depletion or ablation can also compromise axonal morphology. Sigma-1 receptor knockout mice exhibited lower densities of axons, as measured by actin neurofilament immunostaining in the cortex, when compared to wild-type mice [127]. In addition, a slower rate of degradation of p35 was observed when sigma-1 receptors were depleted by knockdown *in vitro* or knockout *in vivo* [127]. P35 is a major activator of cyclin-dependent kinase 5 (cdk5), which plays an important role in cytoskeletal dynamics of microtubules and actin neurofilaments [128]. In contrast, overexpression of sigma-1 receptors in CHO cells resulted in a faster rate of degradation of p35 [127]. The influence of sigma-1 receptors on p35 appears to involve indirect interactions since direct physical interactions were not detected [127]. Notably, myristate was shown to bind to sigma-1 receptors as a putative agonist, resulting in increased phosphorylation of actin neurofilament proteins and myristoylation of p35 within 24 h. This modification of p35 increases its susceptibility to protein degradation [129], thus ultimately eliciting axonal extension in wildtype neurons and rescuing deficits in axonal elongation in sigma-1 knockdown neurons [127]. Together, the data suggest that sigma-1 receptors, in response to stimulation by myristic acid, can influence axonal elongation by modulating p35 turnover.

Collectively, the data suggest that therapeutic interventions that restore sigma-1 receptor expression or stimulate its function can reverse alterations in neuronal structure or morphology that result from or are associated with disease. In this regard, it is noteworthy that administration of the sigma-1 agonist PRE084 restored the deficits in sigma-1 receptor expression in a cellular model of HD, which were accompanied by reductions in a multitude of neurodegenerative markers (Hyrskyluoto et al. 2013). Future investigations to characterize the relationship between sigma-1 receptors and morphological changes in the context of neurodegenerative disease models and treatment, particularly under *in vivo* conditions, would be of value.

10.4.3 Recruitment of New Cells to Damaged Area

Damage to the nervous system is characterized by the loss of neurons, as well as the recruitment of glial cells to the site of injury. In response to CNS injury, sigma-1 agonists have been reported to enhance microglial and astrocytic activities that are associated with repair (see Sects. 10.3.5 and 10.3.6, respectively). Although not yet studied in the context of neurodegeneration, there is some evidence from depression models that sigma-1 agonists promote neurogenesis. For example, the selective sigma-1 agonist SA4503 promoted neurogenesis following subchronic treatment in stress-naive rats [130] and also in calcium/calmodulin-dependent protein kinase IV null mice exhibiting depressive behaviors and impaired neurogenesis [131]. In another animal model of depression involving olfactory bulbectomized mice, sigma-1 active compounds such as dehydroepiandrosterone (DHEA) similarly enhanced neurogenesis [132], an effect that was inhibited by treatment with the sigma-1 antagonist NE-100. In contrast, knockout of sigma-1 receptors in mice suppressed neurite growth and the survival of newborn neuronal

cells in the hippocampal dentate gyrus of adult mice [133]. Finally, stem cells which are under investigation for transplantation procedures [134] are enriched in sigma receptors [135].

10.5 Sigma-1 Receptor Activity as a Signal Amplifier in Neurodegeneration and Neuroprotection

Sigma ligands confer protective effects against many pathological mechanisms of neurodegeneration in preclinical studies, and have yielded great success as neuroprotective agents in different animal models of neurodegenerative disorders. However, the Food and Drug Administration (FDA) has yet to approve a selective sigma ligand for use in humans. In the single clinical study that tested a selective sigma ligand for the treatment of neurodegeneration, the selective sigma-1 agonist SA4503 failed to elicit significant functional recovery in the treated population compared to the placebo control after ischemic stroke [136]. However, post-hoc analysis of moderately and severely affected subjects showed significantly greater National Institutes of Health Stroke Scale improvements in the SA5403-treated group when compared with placebo (P=0.034 and P=0.038, respectively) [136]. Further clinical trials will be needed to optimize patient characteristics to identify a potential responder population, determine appropriate timing for treatment initiation and treatment duration, and evaluate the potential interaction of sigma-1 receptor therapy with other existing conventional pharmacological or non-pharmacological therapies.

It is noteworthy that many currently marketed psychotropic medications have significant affinity for sigma-1 receptors. Whether the therapeutic effects of these medications are mediated by sigma-1 receptor activity in humans remains unclear. Preclinical studies have shown that compounds such as fluvoxamine, DHEA-sulfate (DHEAS) and donepezil do elicit neuroprotective effects in part through activation of sigma-1 receptors, as their effects were attenuated with selective sigma-1 antagonists [13, 28, 137]. Below, we offer the hypothesis that alterations in the function or expression of sigma-1 receptors by themselves will likely be insufficient to cause disease or mitigate neurodegeneration. Rather, sigma-1 receptor dysfunction is likely to worsen disease progression, whereas stimulation may amplify pre-existing functional mechanisms of neuroprotection and/or restoration to slow down the disease progression.

10.5.1 Aberrant Sigma-1 Expression/Structure and Pathogenesis of Neurodegenerative Disease

Several recent studies have shown that decreased expression of sigma-1 receptors may contribute to the pathogenesis of neurodegenerative diseases. Mishina and colleagues, for example, used positron emission tomography (PET) with [^{11}C] SA4530 to demonstrate reduced densities of sigma-1 receptors in the frontal, temporal and occipital lobes, cerebellum, and thalamus of early AD patients [138]. A later study in PD patients showed that the binding potential of the PET ligand [^{11}C]SA4503 to sigma-1 receptors was significantly lower on the more affected than the less affected side of the anterior putamen [139]. However, there was no significant difference with respect to the binding potential between the patients and controls [139]. This supports the model that dysfunction in sigma-1 receptor protein expression augments, rather than initiates, disease progression.

Additionally, mutations in the sigma-1 receptor gene have been reported in ALS [93, 94], and sigma-1 receptor accumulates in intracellular protein aggregates in various neurodegenerative disorders, including trans-activation response DNA protein 43 proteinopathy, tauopathy, alpha-synucleinopathy, polyglutamine disease and intranuclear inclusion body disease [82, 140]. Since sigma-1 receptors have chaperone and regulatory roles [76, 84, 141], this accumulation may reflect a failed adaptive response to clear the inclusions during the course of the various diseases. It remains to be determined, however, whether these accumulations of sigma-1 recep-

tors represent accumulations of unfolded/non-functional or functional sigma-1 receptors. This accumulation may also contribute to disease progression by limiting the number of soluble sigma-1 receptors present in the cell, which may in turn potentiate ER stress and subsequent apoptosis. This suggests that sigma-1 receptor dysfunction is a later effect in the pathologic process, after neurodegeneration has begun but possibly before the manifestation in clinical symptoms. Targeting the remaining functional sigma-1 receptors with sigma-1 agonists may therefore slow down disease progression (see Sect. 10.5.2).

Evidence from sigma-1 receptor knockdown and knockout studies in cellular and animal studies further support this hypothesized contributory role of sigma-1 receptors. In CHO cells, the knockdown of sigma-1 receptors destabilized the conformation of IRE1 and decreased cell survival following administration of the ER stressor thapsigargin [84]. In contrast, under vehicle conditions (in the absence of thapsigargin), sigma-1 knockdown had no effect on the stability of IRE1 or apoptosis [84]. In animal studies, Langa and colleagues demonstrated that homozygous mutant mice (mouse sigma-1 receptor gene, *mSR1−/−*) were viable and fertile with negligible overt phenotype compared with their wildtype littermates [142]. Mavlyutov et al. found that knockout of sigma-1 receptors produced slight motor abnormalities on a rotarod test, but did not itself result in an ALS phenotype or increased weight loss [143]. On the other hand, knockout of sigma-1 receptors in a SOD1-G93A mouse model of ALS exacerbated weight loss, produced an early decline in swimming performance, and ultimately decreased longevity [25].

Supporting the hypothesis that the deleterious consequences of sigma-1 receptor malfunction or aberrant expression manifest primarily under conditions of stress, retinal development also appears normal in sigma-1 knockout mice, with significant deficits (e.g., increased RGC loss and increased intraocular pressure) observed only with advanced age [144, 145]. A recent study showed that RGC death is accelerated in sigma-1 receptor knockout mice compared to wildtype following optic nerve crush, a model system for triggering apoptotic responses similar to those seen in glaucoma [144]. More extensive characterization has also been performed in sigma-1 receptor knockout mice with streptozotocin (STZ)-induced diabetes. Similar to the ocular crush model, STZ treatment accelerated retinal damage in sigma-1 receptor knockout mice; diabetic sigma-1 knockout mice showed fewer RGCs and more caspase-3 positive cells compared to non-diabetic wildtype mice, while sigma-1 knockout alone had no effects [145]. Additionally, relative to the other groups tested (non-diabetic knockout, non-diabetic wildtype and diabetic wildtype), diabetic sigma-1 receptor knockout mice showed increased intraocular pressure and deficits in scotopic threshold responses, which are the most sensitive electroretinogram responses observable with dim stimuli in the dark-adapted state and reflect RGC health [145].

10.5.2 Sigma-1 Activation as Intracellular Amplifier of Pre-existing Neuroprotective Mechanisms

Su and Hayashi proposed that sigma-1 receptors act as intracellular amplifiers for signal transduction, describing the biochemical actions of sigma-1 receptors as modulatory in nature and that the functional implications of these receptors may only be manifested when another biological system is first activated [146]. Consistent with this, the selective sigma-1 agonist (+)-pentazocine prolonged the association of sigma-1 receptors with IP_3 receptors under ER stress but had no effect under normal conditions [76]. Likewise, sigma-1 agonists, without effects by themselves, potentiated bradykinin-induced alterations in cytosolic free Ca^{+2} concentrations [147]. In addition, Monnet and colleagues showed that in anesthetized rats, (+)-pentazocine had no detectable effects on its own, but potentiated NMDA-mediated glutamatergic stimulation [148, 149].

Relevant to neurodegenerative diseases, abnormal intracellular sigma-1 protein aggregates have been reported in various disorders, as

mentioned in Sect. 10.5.1. Specific to ALS, sigma-1 receptor accumulation has been observed in lumbar alpha motor neurons of ALS patients and SOD1-G93A mice, cultured fibroblasts from ALS-8 patients with the P56S-VABP (vesicle-associated membrane protein-associated protein B) mutation, and in NSC34 (mouse motor neuron-like hybrid) cells transfected with the P56S-VABP mutation [140]. These accumulations co-localized with VAPB in the fibroblasts and NSC34 cells with the P56S-VABP mutation [140]. VABP is another ER protein, in which the P56S point mutation causes severe misfolding of the peptide and leads to the formation of cytoplasmic inclusion bodies and familial ALS [140]. Importantly, activation of sigma-1 receptors by PRE084 in P56S-VABP NSC34 cells ameliorated mutant VAPB aggregation and increased the degradation of soluble mutant VAPB without affecting the normal level of the wildtype proteins [140]. These results suggest targeting sigma-1 receptors with agonists can help ameliorate protein aggregation and inhibit disease progression by enhancing their innate chaperone activity.

Relevant to the neurorestorative potential of sigma-1 receptors, in PC12 cells, several sigma-1 agonists including (+)-pentazocine, imipramine, fluvoxamine and donepezil showed no effects on their own but potentiated NGF-induced neurite outgrowth [117–120]. Co-administration of the sigma-1 antagonist NE-100 blocked this effect, confirming the specificity of sigma-1 receptor involvement [117–120]. Moreover, the overexpression of sigma-1 receptors enhanced the NGF-induced neurite sprouting, while antisense deoxyoligonucleotides directed against sigma-1 receptors attenuated the NGF-induced neurite outgrowth [120].

10.5.3 Proposed Use of Sigma-1 Ligands in a Multi-target Therapeutic Approach

Due to the intrinsic modulatory role of sigma-1 receptors in disease and therapy, sigma-1 receptor activation as a stand-alone treatment appears unlikely to be sufficient to elicit observable clinical outcomes. The large body of preclinical evidence using primarily selective sigma-1 compounds described above indicates sigma-1 receptors are viable targets for therapeutic applications for CNS-related disorders. However, to combat the complex and multi-dimensional nature of neurodegenerative diseases, a multi-treatment approach would likely be most beneficial. Sigma-1 ligands, with the ability to affect multiple mechanisms and neural cell types that contribute to neurodegeneration through sigma-1 receptor activation, may therefore offer greater promise as an adjunct therapy. As we mentioned above, though there are no currently approved selective sigma-1 compounds for use in humans, many currently available psychotropic drugs interact with sigma-1 receptors. Using PET with [^{11}C]SA4503, Ishikawa and colleagues showed that fluvoxamine, which has the highest affinity for sigma-1 receptors among SSRIs, binds to sigma-1 receptors in living human brains at therapeutic doses [150]. A follow-up study also showed that the acetylcholinesterase inhibitor donepezil binds to sigma-1 receptors at therapeutic doses [151]. Recently, in a mouse model of amyloid beta (25–35)-induced memory impairments, Maurice showed that protection by the sigma-1 agonist PRE084 is synergistic with donepezil [152]. Therefore, the repurposing or development of sigma-1 receptor active drugs, selective or not, requires further investigation as viable therapeutic approaches for treating neurodegenerative diseases. Moreover, the usage of selective sigma-1 ligands as an adjunct (vs. standalone) treatment may prove more fruitful in clinical trials and serve to validate the potential therapeutic significance of sigma-1 receptors as amplifiers of neuroprotective actions.

10.6 Conclusion

Sigma-1 receptors, with their wide range of effects on multiple signaling pathways, appear to be promising, druggable targets to help combat the complex pathophysiology of neurodegenerative disorders. In its apparent role as an intracel-

lular amplifier, however, sigma-1 receptor activation will likely be most effective in a multi-target therapeutic approach in conjunction with other pharmacological interventions. Further understanding the signaling cascades regulated by sigma-1 receptors will aid in the development of novel therapies to slow the progression of neurodegeneration and/or reverse existing pathologies.

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