Sigma-1 (σ_1) Receptor in Memory and Neurodegenerative Diseases

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Contents

Abstract

The sigma-1 (σ_1) receptor has been associated with regulation of intracellular Ca^{2+} homeostasis, several cellular signaling pathways, and inter-organelle communication, in part through its chaperone activity. In vivo, agonists of the σ_1 receptor enhance brain plasticity, with particularly well-described impact on learning and memory. Under pathological conditions, σ_1 receptor agonists can induce cytoprotective responses. These protective responses comprise various complementary pathways that appear to be differentially engaged

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according to pathological mechanism. Recent studies have highlighted the efficacy of drugs that act through the σ_1 receptor to mitigate symptoms associated with neurodegenerative disorders with distinct mechanisms of pathogenesis. Here, we will review genetic and pharmacological evidence of σ_1 receptor engagement in learning and memory disorders, cognitive impairment, and neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and Huntington's disease.

Keywords
Alzheimer's disease • Amyotrophic lateral sclerosis • Huntington's disease • Learning and memory • Multiple sclerosis • Neuroprotection • Parkinson's disease • σ_1 polymorphisms • σ_1 receptor

1 The Sigma-1 (σ_1) Receptor in Cellular Physiology

The sigma-1 (σ_1) receptor was initially thought to be a subtype of opioid receptors (Martin et al. 1976). It is now clearly defined as a unique membrane-associated protein (Hanner et al. 1996; Schmidt et al. 2016) with chaperone activity (Hayashi and Su 2007). It is expressed in tissue throughout the body including central nervous system (CNS) cells, in neurons, astrocytes, oligodendrocytes, and microglia (Alonso et al. 2000). Its amino acid sequence predicts a 26 kDa protein (Hanner et al. 1996; Schmidt et al. 2016). It is expressed primarily in the intracellular endomembrane networks where it associates with the glucose-related protein 78/binding immunoglobulin protein (GRP78/BiP) (Hayashi and Su 2007). It has been reported to be enriched at mitochondria-associated endoplasmic reticulum (ER) membranes (MAM) (Hayashi and Su 2007) where it regulates interorganelle calcium exchange. It also has been reported to be expressed at the plasma membrane where it associates with ceramide-enriched lipid rafts microdomains (Hayashi and Su 2007, 2003, 2004, 2005, 2010). The σ_1 receptor acts as a chaperone, binding several client proteins.

It can be activated or inactivated by numerous pharmacological compounds, including psychostimulants, antipsychotics, opioids, muscarinic receptor ligands, D2 dopamine receptor ligands, N-methyl-D-aspartate (NMDA) receptor ligands, monoamine transporters inhibitors, serotonin reuptake inhibitors, monoamine oxidase inhibitors, steroids, some peptides like neuropeptide Y, and calcitonin gene-related peptide [reviewed in (Maurice and Su 2009)]. Under physiological conditions, the σ_1 receptor is thought to be associated with the ER-resident chaperone BiP at MAM (Hayashi and Su 2007). Under acute cellular stress or in response to treatment with agonists, the σ_1 receptor dissociates from BiP and binds alternate client or partner proteins including the inositol 1,4,5-trisphosphate (IP_3) receptor, thus enhancing calcium entry into the mitochondria (Hayashi et al. 2000; Hayashi and Su 2007). Ca^{2+} entry into mitochondria promotes redox reactions and ATP production, thereby regulating Ca^{2+}-dependent enzymes in the tricarboxylic acid cycle (Rizzuto et al. 2004). Recently, an alternative mechanism of Ca^{2+} modulation

by the σ_1 receptor has been proposed. Brailoiu et al. (2016) described that the psychostimulant drug cocaine inhibits store-operated Ca^{2+} entry (SOCE), a Ca^{2+} influx mechanism promoted by depletion of intracellular Ca^{2+} stores, in rat brain microvascular endothelial cells through a σ_1 receptor-dependent mechanism. Cocaine-induced SOCE inhibition was blocked by shRNA knockdown of the σ_1 receptor or the σ_1 receptor antagonists BD1063 and NE100. The σ_1 receptor therefore may regulate Ca^{2+} homeostasis by various intracellular signal transduction pathways involving protein–protein interactions. The σ_1 receptor appears to constitute a unique class of protein that influences a range of cellular systems. It has been shown that ectopic overexpression of σ_1 receptor or treatment with σ_1 receptor agonists can counteract ER stress, whereas decreasing its expression enhances apoptosis (Hayashi and Su 2007). In addition, after activation, σ_1 receptor can translocate to the plasma membrane or other cell compartments and bind to various receptors and membrane-associated proteins, including ion channels, kinases, G-protein coupled receptors, or trophic factor receptors (Martina et al. 2007; Navarro et al. 2010, 2013; Kourrich et al. 2013).

Among other effects with evident physiological impacts on brain plasticity and memory, activation of the σ_1 receptor modulates voltage-gated ion channels involved in the initiation and shaping of action potentials (Soriani et al. 1999; Zhang and Cuevas 2002), NMDA-induced neuronal firing in the hippocampus (Monnet et al. 1990; Martina et al. 2007), and recruitment and coupling of Ca^{2+}-dependent nitric oxide synthase (NOS) to postsynaptic density protein-95 (PSD95) (Cao et al. 2005; Yang et al. 2010). The σ_1 receptor is also able to shape cellular plasticity in neuronal cells by directly modulating the activity of pleiotropic transcription factors such as nuclear factor κB (NFκB), cyclic adenosine monophosphate (cAMP) response element-binding (CREB) protein, and c-fos. These transcription factors are involved in the modulation of pro- and anti-inflammatory genes as well as cell death and survival (Meunier and Hayashi 2010). At the plasma membrane, the σ_1 receptor may directly control dendritic spine arborization by increasing Rac-GTP, in part by regulating levels of intracellular reactive oxygen species (ROS) (Tsai et al. 2009). A direct interaction between the σ_1 receptor and Rac1-GTPase was described in brain mitochondria (Natsvlishvili et al. 2015). The σ_1 receptor therefore constitutes a unique class of proteins influencing and participating in a wide range of biological pathways, including Ca^{2+} signaling at the ER and controlling several families of ion channels at the plasma membrane and MAM. The σ_1 receptor helps to maintain ER-mitochondria exchanges and trigger transcription factor expression. The σ_1 receptor-mediated neuromodulation, affecting several cellular pathways, has an important role on brain plasticity either in physiological conditions, particularly learning and memory processes, or on brain preservation, particularly during neurodegenerative insults.

2 Role of σ_1 Receptors in Learning and Memory

Agonists of the σ_1 receptor are effective anti-amnesic compounds. This has been demonstrated in a number of pharmacological and pathological models of learning and memory impairment in rodents. In particular, new σ_1 agonists are routinely validated in vivo against scopolamine-induced learning deficits, a model of muscarinic acetylcholine receptor (mAChR) blockade. For instance, the σ_1 receptor agonist LS-1-137, an *N*-(1-benzylpiperidin-4-yl)phenylacetamide analog (Malik et al. 2015), the σ_1 receptor agonist (4R,5S)-2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide [E1R; (Zvejniece et al. 2014)], or the mixed mAChR/σ_1 receptor agonists ANAVEX1-41 or ANAVEX2-73, two diphenyl-3-furanmethanamine derivatives (Espallergues et al. 2007; Villard et al. 2009) have recently been characterized as anti-amnesic drugs against scopolamine-induced learning impairment. The efficacy of σ_1 receptor agonists as symptomatic drugs in cognition has been described not only in cholinergic amnesia models (e.g., scopolamine, mecamylamine, *p*-chloroamphetamine, forebrain lesions) but also in glutamatergic models of learning deficit. Learning impairment induced by the noncompetitive NMDA receptor antagonist dizocilpine (MK-081) has been used to demonstrate that the positive modulation exerted by the σ_1 receptor on NMDA neurotransmission, suggested in vitro (Monnet et al. 1992b, 1995) and in vivo using extracellular recordings of the NMDA-induced firing of pyramidal neurons in the CA3 hippocampal area (Monnet et al. 1990, 1992a), has behavioral consequences. The efficacy of σ_1 receptor agonists in alleviating dizocilpine-induced learning impairment also points to the potential utility of these drugs in treating schizophrenia-related cognitive deficits, in particular since hypoglutamatergy models have been considered as highly pertinent for mimicking the negative symptoms of schizophrenia (Meltzer et al. 2013). Interestingly, σ_1 receptor ligands tested in both the scopolamine and dizocilpine models showed a similar active dose-range in vivo (Villard et al. 2009, 2011). Activation of the σ_1 receptor therefore appeared to similarly modulate the activity of the two neurotransmission systems involved in memory processes in the limbic and cortical structures, namely the cholinergic and glutamatergic systems.

The cholinergic system is crucial for learning, consolidation, and retrieval phases of the memory processes. Cholinergic basal forebrain neurons in the *nucleus basalis magnocellularis* innervate the cerebral cortex, amygdaloid complex, and hippocampus, all structures involved in memory formation (Aigner 1995). Activation of σ_1 receptors by agonists provokes ACh release. This has been shown both in vitro and in vivo. (+)-SKF-10,047, igmesine, and cutamesine (SA4503) potentiate KCl-induced release of [^{3}H]-ACh from rat hippocampal slices (Junien et al. 1991; Horan et al. 2002). (+)-SKF-10,047, (+)-3-PPP, (+)-pentazocine, DTG, and cutamesine acutely and dose-dependently increase extracellular ACh levels in the frontal cortex and hippocampus as measured by in vivo microdialysis in freely moving rats (Matsuno et al. 1993, 1995). The mechanism by which these σ_1 receptor ligands induce ACh release involves Ca^{2+} mobilization through IP_3 receptor and voltage-gated K^+ and Ca^{2+} channels (Hayashi et al. 2000; Foskett et al. 2007).

Some σ_1 receptor agonists enhance NMDA-induced firing in the hippocampus at very low doses (Monnet et al. 1990, 1992a, b, 1995). Neuroactive steroids with affinity for σ_1 receptors such as dehydroepiandrosterone (DHEA) sulfate or pregnenolone sulfate enhanced paired-pulse facilitation or facilitate induction of frequency-dependent long-term potentiation (LTP) in rat hippocampal CA1 pyramidal cells (Schiess and Partridge 2005; Chen et al. 2006). The latter effect was proposed to involve Src-dependent NMDA receptor signaling and regulation of the tyrosine phosphorylation of NMDA receptor subunit 2B (NR2B). Tyrosine phosphorylation of NR2B decreased after reversible forebrain ischemia in rats and improved after repetitive administration of DHEA sulfate, whereas NR1 remained unchanged (Li et al. 2006). Moreover, (+)-SKF-10,047, PRE-084, and (+)-pentazocine increased the expression of NR2A and NR2B, as well as PSD95, in the rat hippocampus (Pabba et al. 2014). Treatment with σ_1 receptor agonists leads to increased interaction between NR2 subunits and σ_1 receptors and promotes trafficking of NMDA receptors to the cell surface. The σ_1 receptor interacts with NMDA receptors through the regulation of a small conductance Ca^{2+}-activated K^+ current (SK channels). Using patch-clamp whole-cell recordings in CA1 pyramidal cells of rat hippocampus, Martina et al. (2007) described that (+)-pentazocine potentiated NMDA receptor responses and LTP by preventing the opening of SK channels, a channel known to shunt NMDA receptor responses. These electrophysiological parameters were examined in σ_1 receptor knockout (*SIGMAR1* KO) mice. Using whole-cell patch-clamp recordings from CA1 pyramidal neurons, Snyder et al. (2016) observed no change in action potential or basic cellular characteristics and no change in presynaptic function, as indicated by a similar paired-pulse ratio and miniature excitatory postsynaptic current frequency. The AMPA and NMDA receptors were unaffected, with no difference in AMPA/NMDA ratio or decay kinetics, in *SIGMAR1* KO compared to wild-type mice (Snyder et al. 2016). However, a small but significant reduction in the magnitude of LTP was measured, suggesting that basic cellular physiology is unaffected after σ_1 receptor ablation, but the neuronal network is partially compromised. At the behavioral level, young male *SIGMAR1* KO mice, at 2 months of age, showed signs of anxiety in procedures including the open-field, passive avoidance and elevated plus-maze, and an enhanced response to stress in the forced swim test (Chevallier et al. 2011). In male animals, the σ_1 receptor ablation therefore increased stress and anxiety responses but memory responses were unchanged. However, female *SIGMAR1* KO mice showed memory alterations in spontaneous alternation and water-maze learning paradigms, and this phenotype increased with age. Of note, both 2- and 14-month old female *SIGMAR1* KO mice showed decreased plasma levels of 17β-estradiol and a supplementation treatment with the hormone reversed the memory deficits in young and aged mice (Chevallier et al. 2011). This suggested that σ_1 receptor ablation has a developmental impact on the steroidal tonus.

Agonists of the σ_1 receptor are promising symptomatic drugs in rodent models of cognitive alterations related to pathological aging and neurodegenerative diseases. First, igmesine and PRE-084, in the low mg/kg dose-range, improved learning ability in the senescence-accelerated mouse SAMP/8 (Maurice et al. 1996). Second,

these compounds also alleviated the memory deficits induced by amyloid toxicity in pharmacological models of Alzheimer's disease (AD). (+)-pentazocine, PRE-084, cutamesine, dimemorphan, ANAVEX1-41, ANAVEX2-73, and σ_1 receptor binding neuroactive steroids attenuated learning deficits in mice that received a direct intracerebroventricular injection of oligomerized $A\beta_{25\text{-}35}$ peptide, which produces neurotoxicity closely related to AD pathology (Maurice et al. 1996; Zussy et al. 2011). All σ_1 receptor agonists alleviated the $A\beta_{25\text{-}35}$-induced learning impairments in spatial or nonspatial tasks involving short-term as well as long-term memory. These effects were blocked by BD1047, haloperidol, BMY-14,802, and progesterone, all putative σ_1 receptor antagonists (Maurice et al. 1998; Wang et al. 2003; Espallergues et al. 2007; Villard et al. 2009; Yang et al. 2012; Maurice 2016). Of note, whereas they blocked σ_1 receptor agonist effects, the antagonists alone did not alter behavior (positively or negatively) in these models. Agonists of the σ_1 receptor are thus promising agents to treat AD symptoms, with active doses similar to or lower than the reference drugs such as rivastigmine, galantamine, and memantine (Meunier et al. 2006). The symptomatic efficacy of these compounds remains to be confirmed in a transgenic mouse model of AD.

3 Genetic Evidence in Support of a Role for σ_1 Receptors in Neurodegenerative Diseases

The gene encoding the human σ_1 receptor, *SIGMAR1*, is located on chromosome 19 band p13 and contains four exons and three introns. Polymorphisms have been identified that link *SIGMAR1* to vulnerability to or protection against neurological and psychiatric diseases. First, an association with a genetic variant of the σ_1 receptor carrying the mutation E102Q and juvenile amyotrophic lateral sclerosis (ALS) was observed in a consanguineous family, with an autosomal recessive pattern (Al-Saif et al. 2011). This highly conserved mutation among patients is located within a predicted transmembrane domain of the σ_1 receptor. Expression of $SIGMAR1^{E102Q}$ in NSC34 motor neuron-like cells revealed aberrant subcellular distribution of the mutated protein, and cells expressing the mutant protein were more sensitive to apoptosis induced by ER stress (Al-Saif et al. 2011). However, another report suggested that impact of mutations in σ_1 receptor may not be so common in ALS, since only one mutation, T58C, present in the 3′-untranslated region, was identified in a population of 728 Korean ALS patients (Kim et al. 2014). The latter report questioned the causative role of σ_1 receptor mutations in ALS.

Luty et al. (2010) identified, in Australian and Polish patients with frontotemporal lobar degeneration (FTLD) and motor neuron disease (MND), a nonpolymorphic mutation (c.672*51G>T) in the 3′-untranslated region of *SIGMAR1* that increased *SIGMAR1* transcripts in lymphocytes and brain tissue. A morphological examination of the hippocampus showed that overexpression of the σ_1 receptor shunted TDP-43 and fused-in-sarcoma (FUS) proteins from the nucleus to the cytoplasm by 2.3- and 5.2-fold, respectively. Treatment of SK-NMC and SK-N-SH cells with σ_1 receptor ligands significantly altered translocation of TDP-43. The authors concluded that

SIGMAR1 may be a causative gene for familial FTLD-MND with a unique neuropathology that differs from other FTLD and MND cases, and that σ_1 receptor drugs may be potential therapeutic agents for TDP-43/FUS proteinopathies (Luty et al. 2010).

Several studies have suggested links between two polymorphisms identified in populations from different origin and the vulnerability to AD: G241T/C240T and Q2P (Uchida et al. 2005; Huang et al. 2011; Feher et al. 2012). In a population of 239 Japanese patients with AD, these two polymorphisms were in complete linkage disequilibrium with each other resulting in two haplotypes: GC241-240/Q2 and TT241-240/P2. The TT241-240/P2 homozygosity of the *SIGMAR1* gene significantly reduced the risk of AD in apolipoprotein E (apoE) ε4 carriers, suggesting a protective role for this haplotype in AD (Uchida et al. 2005). In a study involving 322 Hungarian late-onset AD patients and 250 elderly control individuals, the polymorphisms also appeared in nearly complete linkage disequilibrium resulting in the two previously observed predominant haplotypes (Feher et al. 2012). An association between the TT241-240/P2 variant and the risk for developing AD was observed. A potential modest interaction of the co-presence of this haplotype with apoE ε4 allele was noted on the risk for AD (Feher et al. 2012). In a study involving an Australian cohort with 82 AD subjects and a Chinese cohort with 330 cases, a significant genetic interaction was found between the apoE ε4 carriers and the P2 haplotype in both populations (Huang et al. 2011). In non-ApoE ε4 carriers, patients with the P2 variant had increased cognitive dysfunction and more neurofibrillary tangles, indicative of an advanced stage of AD. However, in a group of 219 Polish patients with late-onset AD, no significant difference for the *SIGMAR1* allele, genotype, haplotype, and diplotype distributions was observed as compared with the control patients group. Moreover, no interaction with apoE ε4 carriers was found (Maruszak et al. 2007).

Polymorphisms and association analyses have suggested possible interactions in other neuropsychiatric diseases. In a Japanese population, Kishi et al. (2010) described a genetic association between *SIGMAR1* and major depressive disorder (MDD). After selecting the single nucleotide mutation rs1800866 (i.e., the Q2P genotype) in *SIGMAR1* for association analysis, they detected an association of the phenotype (MDD or controls) with the Q2P genotype. However, they found no association between response to serotonin reuptake inhibitor antidepressant treatment and the Q2P genotype. However, the observation suggested that the Q2P genotype may play a role in the pathophysiology of MDD in the Japanese population (Kishi et al. 2010).

Contradictory results have been reported regarding *SIGMAR1* polymorphisms and schizophrenia. Three early studies presented negative results. Ohmori et al. (2000) reported no significant difference in the distribution of the G241T and G240T polymorphisms among 129 schizophrenic patients and 140 controls. Uchida et al. (2003) described no significant association between *SIGMAR1* and schizophrenia in a meta-analysis comprising 636 schizophrenic and 779 control subjects that included previous studies and a case-control association study, between two polymorphisms of *SIGMAR1*, G-241T/C-240T and Q2P, and schizophrenia in a Japanese population. Satoh et al. (2004) analyzed the distribution of *SIGMAR1*

polymorphisms in 100 schizophrenic and 104 control subjects and no significant association was found between the T-485 A, GC-241–240TT, Q2P, and G620A (A211Q) variants and schizophrenia and clinical characteristics. However, more recently, two studies reported evidence in support of an association between the Q2P polymorphism and schizophrenia in Japanese populations. First, Takizawa et al. (2009) analyzed 40 schizophrenic patients and 60 healthy control subjects. In schizophrenics, even after controlling for the effect of medication, the hemodynamic response in the prefrontal cortex of the Q2 genotype group was significantly greater than that of the P2 carriers. Clinical symptoms were, however, not different between the two genetic subgroups. Second, Ohi et al. (2011) did a meta-analysis of the association between the functional Q2P polymorphism and schizophrenia using combined samples, 1,254 schizophrenic patients and 1,574 healthy control subjects from previously published studies, and an additional sampling of 478 patients and 631 controls. They reported evidence in support of an association between Q2P and schizophrenia, without heterogeneity across studies. Patients with schizophrenia showed lower bilateral activation of the prefrontal cortex and P2 carriers had significantly lower activation of the right prefrontal cortex, compared to subjects with the Q2 genotype. Additional evidence, particularly in ethnically diverse populations, is needed. However, these recent studies suggest that certain *SIGMAR1* polymorphisms could be associated with an increased risk of schizophrenia.

Finally, the T485A polymorphism has been implicated in alcoholism. In a population of 307 alcoholic patients and 302 control subjects, Miyatake et al. (2004) observed that the transcriptional activity of the A485 allele and the TT241-240 allele was significantly reduced compared with that of the T485 allele and the GC241-240 allele and that the frequencies of the A485 allele and the TT241-240/P2 haplotype were significantly higher in control subjects compared with alcoholic subjects. They concluded that T485A and GC241-240TT may be functional polymorphisms, and the A485 allele and TT241-240/P2 haplotype are possible protective factors in the development of alcoholism (Miyatake et al. 2004).

4 Pharmacological Evidence That σ_1 Receptor Ligands Engage Neuroprotective Mechanisms in Neurodegenerative Disease

4.1 Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia in the world. According to the World Health Organization, 47.5 million people have dementia, and 7.7 million new cases appear per year. By 2025, the number of people aged 65 and older with AD is estimated to reach 7.1 million in the USA (data from the Alzheimer's Association). AD is clinically characterized by progressive cognitive impairment evolving towards dementia and death. At the physiopathological level, the presence of extracellular senile plaques composed primarily of amyloid-β peptide (Aβ) and the intracellular accumulation of neurofibrillary tangles, due to

aggregation of hyper- and abnormally phosphorylated Tau protein signal the disease and contribute to its complex pathogenesis (Selkoe 2004). Neurodegeneration indeed involves complex synergies between oxidative stress and mitochondrial dysfunction, proteotoxic and cellular stress, calcium imbalance, neuroinflammation, hypoxia, DNA damage, synaptic alterations, and apoptosis. Clinically, the diagnosis is mainly based on cognitive evaluation using the mini-mental status examination (MMSE) score, but magnetic resonance imaging (MRI) of hippocampal volume, visualization of plaques using positron emission tomography (PET), and analyses of blood markers like Aβ species or phosphorylated forms of Tau are being developed as diagnostic tools. With regard to treatment, only symptomatic therapies are currently available for AD. Standard medical treatments include the cholinesterase inhibitors donepezil, rivastigmine, galantamine, or the noncompetitive NMDA receptor antagonist memantine. Psychotropic medications are used to treat secondary symptoms of AD, such as depression, agitation, and sleep disorder. More effective therapeutic agents are needed, and σ_1 receptor ligands may meet some of these needs. However, a better understanding of the σ_1 receptor in the context of AD pathophysiology will be crucial for the discovery and development of effective and potentially curative treatment strategies.

Curative treatment must simultaneously block Aβ species generation (leading ultimately to the formation of senile plaques), prevent the hyperphosphorylation of Tau (responsible for the intracellular accumulation of neurofibrillary tangles), preserve mitochondrial integrity, boost neuritogenesis and dendrite connectivity, and stimulate neurogenesis to repopulate neuronal cells and maintain circuitry. Current medications based on cholinesterase inhibitors or the NMDA receptor antagonist have only demonstrated moderate efficacy in symptom management. A first achievement to enlarge the therapeutic means in AD would be to establish an effective neuroprotective agent. Depending on their impact on Aβ load and Tau hyperphosphorylation, such a compound may help to preserve brain structural integrity and restore altered clearance systems for aggregated amyloid and Tau species. It must, however, present a sufficiently wide mechanism of action to be able to significantly attenuate neurodegenerative disease associated oxidative stress, neuroinflammation, hypoxia, apoptotic pathways, and other processes. Since activation of the σ_1 receptor results in modulation of numerous cytoprotective pathways, σ_1 receptor agonists appeared as promising candidates and, indeed, some of them demonstrated neuroprotective properties in preclinical experimental models of AD. In vitro, the selective σ_1 receptor agonists PRE-084 and (−)-MR22 prevented $A\beta_{25\text{-}35}$-induced toxicity in rat neuronal cultures (Marrazzo et al. 2005). Afobazole, a mixed σ_1 and σ_2 receptor ligand, inhibited the $[Ca^{2+}]_i$ increase in rat cortical neurons after prolonged exposure to $A\beta_{25\text{-}35}$ (Behensky et al. 2013). Afobazole decreased nitric oxide (NO) production in response to $A\beta_{25\text{-}35}$, but did not affect the increase in ROS. The reductions in $[Ca^{2+}]_i$ and NO levels by afobazole were associated with a decrease in neuronal cell death, decreased expression of pro-apoptotic proteins Bax and caspase-3, and increased expression of the anti-apoptotic protein, Bcl-2 (Behensky et al. 2013). Interestingly, microglia also play an important role in σ_1 receptor-mediated cytoprotection against $A\beta_{25\text{-}35}$

toxicity in vitro (Behensky et al. 2013). Treatment with afobazole decreased microglial activation in response to Aβ, as indicated by reduced membrane ruffling and cell migration. It protected against cell death and against the induction of Bax and caspase-3 elicited by prolonged exposure of microglia to $A\beta_{25\text{-}35}$. Afobazole also prevented the decrease in ATP observed in microglia after a 24 h exposure to $A\beta_{25\text{-}35}$. These cytoprotective activities of afobazole were mediated in part by the σ_1 receptor and potentially through purinergic receptors as well (Behensky et al. 2013). These observations support the notion that the cytoprotective effects of targeting the σ_1 receptor not only involve multiple transduction systems and cellular organelles, but also regulate different cellular responses in neuronal and glial cells.

In vivo, the σ_1 receptor agonists PRE-084, (−)-MR22, ANAVEX1-41, ANAVEX2-73, DHEA, DHEA sulfate, and pregnenolone sulfate were neuroprotective in pharmacological models of AD (Meunier et al. 2006; Villard et al. 2009, 2011; Aly et al. 2011; Antonini et al. 2011; Yang et al. 2012; Lahmy et al. 2013). These σ_1 receptor ligands were administered either acutely before or chronically after injection of the pharmacological toxicant ($A\beta_{25\text{-}35}$ peptide or aluminum chloride). The Aβ peptide was injected either intracerebroventricularly or locally into the hippocampal formation, and alone or combined with 192 IgG-saporin, to induce a more severe cholinergic lesion (Antonini et al. 2011). Learning impairment was prevented or attenuated in these models. These beneficial effects were accompanied by neuroprotection. Markers of oxidative stress, cholinergic tonus, neuroinflammation, induction of apoptotic pathways, and cell loss were attenuated by the σ_1 receptor agonists (Meunier et al. 2006; Villard et al. 2009, 2011; Aly et al. 2011; Antonini et al. 2011; Yang et al. 2012). In two studies, the selective σ_1 receptor agonists (−)-MR22 and PRE-084 significantly prevented APP and $A\beta_{1\text{-}42}$ accumulation in the brain following 192 IgG-saporin and/or $A\beta_{25\text{-}35}$ injection (Antonini et al. 2011; Lahmy et al. 2013). Lahmy et al. (2013) also examined activation of the main kinase involved in Tau hyperphosphorylation, glycogen synthase kinase 3β (GSK-3β), and the level of hyperphosphorylated Tau at physiological or pathological epitopes in $A\beta_{25\text{-}35}$-treated mice. PRE-084 and ANAVEX2-73 decreased GSK-3β activation and Tau hyperphosphorylation. Moreover, Fisher et al. (2016) very recently reported that AF710B, a mixed M1 mAChR/σ_1 receptor agonist, administered at 10 μg/kg for 2 months to female 3xTg-AD mice, attenuated learning impairment in the water-maze, decreased BACE1 levels, GSK3β activity, p25/CDK5 levels, and neuroinflammation. AF710B also diminished soluble and insoluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ accumulation, the number of plaques, and Tau hyperphosphorylation (Fisher et al. 2016). These observations suggested that chronic treatment with a σ_1 receptor agonist can alleviate accumulation of amyloid species and hyperphosphorylated Tau, a prerequisite for an effective neuroprotective and disease-modifying therapeutic agent in AD. Further studies with transgenic animal models will be important to confirm this promising observation with AF710B.

An endogenous ligand for the σ_1 receptor remains unknown. In light of the shifting paradigm that the σ_1 receptor may actually be a chaperone and not a receptor *stricto* sensu, it is conceivable that the assumption that the σ_1 receptor should have a traditionally defined endogenous ligand may be inaccurate.

Nevertheless, several endogenous molecules such as neuropeptides, neurosteroids, and the trace amine *N*,*N*-dimethyltryptamine (Su et al. 1988; Fontanilla et al. 2009) or even physiological changes, like oxidative stress (Meunier and Hayashi 2010) and endoplasmic reticulum (ER) stress (Hayashi and Su 2007), also have been shown to trigger σ_1 receptor activation. This raises the question of whether the σ_1 receptor functions as an endogenous neuroprotection system. To address this question, we combined invalidation of σ_1 receptor expression (using *SIGMAR1* KO mice or repeated NE100 treatment) and induction of amyloid toxicity (using $A\beta_{25\text{-}35}$ injection or cross-breeding with APP_{Swe} mice to generate APP_{Swe}/*SIGMAR1* KO mice) (Maurice et al. 2010, 2015). The intracerebroventricular injection of $A\beta_{25\text{-}35}$ peptide provoked learning deficits and oxidative stress in the hippocampus at lower doses in *SIGMAR1* KO mice compared to wild-type animals (Maurice et al. 2010). When σ_1 receptor expression was absent in APP_{Swe}/*SIGMAR1* KO mice, animals showed significantly decreased survival compared with APP_{Swe} mice, *SIGMAR1* KO mice, and wild-type animals. The spontaneous alternation response of APP_{Swe}/*SIGMAR1* KO animals was lower than single transgenic and control lines between 2 and 12 months of age. Eight-month-old APP_{Swe}/*SIGMAR1* KO mice showed impaired place learning in the water-maze and increased ROS level in the hippocampus, but expression of hippocampal synaptic markers (PSD95, synaptophysin) was unchanged (Maurice et al. 2015). Therefore, it appears that the absence of σ_1 receptor can worsen Aβ toxicity and behavioral deficits.

It must be noted that Yin et al. (2015) reported different results. The authors injected $A\beta_{25\text{-}35}$ in heterozygous *SIGMAR1* KO mice and reported that the peptide injection impaired spatial memory and caused cell death of pyramidal cells in the hippocampal CA1 region of wild-type mice, whereas it did not cause such impairments in heterozygous *SIGMAR1*$^{+/-}$ mice. $A\beta_{25\text{-}35}$ injection in wild-type mice modified the levels of NMDA-activated currents and NR2B phosphorylation in the hippocampal CA1 region in an NE100-sensitive manner. However, the $A\beta_{25\text{-}35}$ injection in *SIGMAR1*$^{+/-}$ mice induced a slight increase in NMDA-activated currents and NR2B phosphorylation. Treatment with PRE-084 caused the same changes in NMDA-activated currents and NR2B phosphorylation as those in $A\beta_{25\text{-}35}$-treated wild-type or *SIGMAR1*$^{+/-}$ mice. These results suggested that partial ablation of σ_1 receptor can reduce $A\beta_{25\text{-}35}$-induced neuronal cell death and cognitive deficits by suppressing $A\beta_{25\text{-}35}$-enhanced NR2B phosphorylation. However, the report by Yin et al. (2015) is not in complete contradiction with Maurice and colleagues (2010, 2015), since Yin et al. did not use homozygous *SIGMAR1* KO mice, which present no σ_1 receptor expression in the forebrain. Rather, these data suggest that the impact of the σ_1 receptor on amyloid toxicity could be complex, depending on levels of σ_1 receptor expression and activity.

Although there is growing evidence in support of the σ_1 receptor as a therapeutic target in AD, the impact of the pathology on the expression level of σ_1 receptor is still poorly documented, particularly in terms of precise densities in the vulnerable brain structures and during the different phases of the disease. Using autoradiography and the non-selective σ_1/σ_2 receptor ligand ^{3}H-DTG, a significant 26% loss of

binding sites was noted in the CA1 *stratum pyramidale* region of the hippocampus of AD patients as compared to healthy controls (Jansen et al. 1993). The loss of σ_1/σ_2 sites correlated with a 29% loss of pyramidal cells. Then, a loss of σ_1 sites was observed using PET imaging in the brain of AD patients (Mishina et al. 2008). The binding potency of ^{11}C-SA4503 was reduced in the frontal lobe, temporal lobe, occipital lobe, cerebellum, and thalamus of early AD patients compared to healthy control subjects, however, this was not observed in the hippocampus (Mishina et al. 2008). It therefore appears that in AD, a decreased level of σ_1 receptor in certain brain regions is associated with specific cell loss in vulnerable cell populations in those regions. However, correlation between the decrease in σ_1 receptor binding potency and pathological stage or its response to a σ_1 receptor agonist-based treatment has not been established.

4.2 Parkinson's Disease

Parkinson's disease (PD) is a progressive multi-system neurodegenerative disease affecting people mainly in later years of life. The prevalence of PD in developed countries is generally estimated at 0.3% of the population and about 1% in people over 60 years of age (de Lau and Breteler 2006). The prevalence increases with age both for men and women (de Rijk et al. 1997). The disease is characterized by specific neuropathological hallmarks. There is formation of abnormal spherical bodies mainly composed of α-synuclein protein, named Lewy bodies, and spindle- or thread-like Lewy neurites in the neuronal soma, starting at precise induction sites and progressing in a topographically predictable sequence within the brain (Braak et al. 2004). Degeneration of dopaminergic nigrostriatal neurons presenting Lewy bodies is regarded as the primary neuropathological correlate of motor impairment in PD, but glutamatergic, cholinergic, GABAergic, tryptaminergic, noradrenergic, and adrenergic neurons may show similar intracellular damage (Braak and Braak 2000). A key pathological factor of PD is mitochondrial dysfunction which is closely related to increased ROS formation. Complex I deficiencies of the respiratory chain account for the majority of unfavorable neural apoptosis generation and are considered one of the primary sources of ROS in PD. It has also been reported that genetic mutations in proteins including α-synuclein, parkin, and phosphatase and tensin homolog induced putative kinase (PINK) are linked to the familial forms of PD. Mutations of these genes have been known to affect mitochondrial function and increase oxidative stress. The exact cause is still undetermined and, although there is presently no cure, treatments such as medication and surgery are used to manage its symptoms (Sveinbjornsdottir 2016). The clinical symptoms in PD are usually defined by motor disturbances but there may be disturbances in several other functions of the nervous system. The symptoms are categorized into motor and non-motor symptoms, and some of them may be provoked or aggravated by the dopaminergic treatment (Sveinbjornsdottir 2016). Evidence that σ_1 receptor activity impacts dopaminergic neurotransmission was initially described in the mid-1980s (Freeman and Bunney 1984; Wachtel and White 1988). More recently,

the σ_1 receptor has been shown to bind dopaminergic psychostimulants such as cocaine and methamphetamine and to be involved in their behavioral and cellular effects including hyperactivity, addiction, and neurotoxicity [for reviews, see (Maurice et al. 2002; Maurice and Romieu 2004; Maurice and Su 2009; Yadid et al. 2010; Robson et al. 2012)]. Analyses of the cellular role of σ_1 receptors in DA neurons confirmed their interest in PD. For instance, Mori et al. (2012) described an association between σ_1 receptors and dopamine (DA)-induced cytotoxicity in Chinese hamster ovary (CHO) cells. Physiologically relevant concentrations of DA provoked apoptosis in *SIGMAR1* knockdown CHO cells and a synergistic conversion of nuclear factor κB (NF-κB) p105 to its active form p50, known to down-regulate the transcription of the anti-apoptotic factor Bcl-2 (Mori et al. 2012). Endogenous σ_1 receptors therefore tonically inhibit the proteasomal conversion/activation of NF-κB induced by physiological DA, suggesting that the σ_1 receptor may be a therapeutic target for the treatment of PD. The mapping of σ_1 receptors in PD was reported by Mishina et al. (2005), using PET imaging with [^{11}C]SA4503. The authors assessed whether σ_1 receptors are altered in the damaged dopaminergic system. The binding potential of [^{11}C]SA4503 appeared significantly lower in the more damaged side of the anterior putamen but with no BP difference between PD patients and controls. DA release was therefore reduced asymmetrically in the putamen of early PD. The authors suggested that [^{11}C]SA4503 PET could be an indicator of presynaptic dopaminergic damage in PD (Mishina et al. 2005). In a recent report, Francardo et al. (2014) treated mice presenting a striatal lesion with 6-hydroxydopamine (6-OHDA), a pertinent pharmacological model of PD, with the σ_1 receptor agonist PRE-084. At 0.3 mg/kg, the drug produced a gradual improvement of spontaneous forelimb use. The behavioral recovery paralleled the increase in DA fiber density in the denervated striatum, a modest recovery of DA levels, and an upregulation of BDNF and GDNF neurotrophic factors and their downstream effectors ERK1/2 and Akt (Francardo et al. 2014). No effect of PRE-084 treatment was observed in *SIGMAR1* KO mice lesioned with 6-OHDA, confirming the pharmacology. Interestingly, σ_1 receptor immunoreactivity was observed in astrocytes and neurons in the substantia nigra and striatum and its intracellular distribution was modified by PRE-084. The σ_1 receptor therefore appeared to regulate an endogenous neuroprotection mechanism and restorative plasticity in experimental PD, suggesting therapeutic potential for effective σ_1 receptor agonists.

However, Hong et al. (2015) reported contradictory results using the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model in mice, a mitochondrial neurotoxicant targeting nigrostriatal DA neurons. The authors proposed that σ_1 receptor *deficiency* could reduce MPTP-induced death of dopaminergic neurons through suppression of NMDA receptor function and DA transporter expression. They used heterozygous and homozygous *SIGMAR1* KO (*SIGMAR1*$^{+/-}$ and *SIGMAR1*$^{-/-}$, respectively) mice and observed that MPTP treatment for 5 weeks in wild-type mice caused motor deficits and DA neurons death in substantia nigra *pars compacta* with an increase in NMDA receptor NR2B phosphorylation. This was not observed in *SIGMAR1* KO mice. The σ_1 receptor antagonist NE100 or the NR2B inhibitor

Ro25-6981 alleviated the motor deficits and death of DA neurons in MPTP-treated wild-type mice. But (MPTP + PRE-084)-treated *SIGMAR1*$^{+/-}$ mice showed similar motor deficits and loss of DA neurons as MPTP-treated wild-type mice. Pharmacological and genetic inactivation of σ_1 receptor suppressed the expression of DA transporter in substantia nigra, and it was corrected by NMDA. PRE-084 enhanced DA transporter expression in wild-type mice or *SIGMAR1*$^{+/-}$ mice (Hong et al. 2015). These data, which contradicted all the previously reported cellular and pharmacological observations, were obtained in a different model as used by Francardo et al. (2014). Since MPTP is a mitochondrial toxicant, a putative direct or indirect interaction of MPTP with σ_1 receptor, localized preferentially at the mitochondria-associated ER membranes (MAM) (Hayashi and Su 2007) and therefore impacting directly mitochondrial physiology, could explain these results. A further characterization of the model is therefore necessary to reconcile the data of Hong et al. (2015) and Francardo et al. (2014).

However, σ_1 receptor agonists appear as the most promising agents for developing neuroprotective treatment strategies, particularly in PD. As it has been reported in animal models, σ_1 receptor ligands are effective in early stages of the disease. It will be important to study what happens in later stages of disease that might shift, inactivate, or otherwise change response of the receptor: is it due to inactivation/involvement of σ_1 receptor in different biochemical process or due to other changes in the cells' requirements of σ_1 receptors associated with progression of the pathology? Furthermore, what is the role of σ_1 receptor in prodromal/preclinical markers of PD, non-motor, extra-nigral symptoms including olfactory and autonomic dysfunctions or cognitive and sleep disturbances?

4.3 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is the most widespread type of motor neuron disease and has become the third most common neurodegenerative disease in the world (Logroscino et al. 2010). It is a fatal condition clinically presented by progressive weakness, atrophy, and spasticity of muscle tissue reflecting the degeneration of both upper and lower motor neurons in the cortex, brainstem, and spinal cord. There has been no effective therapeutic approach to halt the progression of the disease so far. Currently, symptom management treatments directed at the clinical manifestation of the disease are the only available ALS therapies. Riluzole, a drug that reduces the levels of excitatory neurotransmitter glutamate, is one of the medications which is able to give several months of extended life to patients with ALS (Cheah et al. 2010). Presentation, course, and progression of ALS are heterogeneous. Most cases of the disease are diagnosed based on symptoms, physical signs, electromyography, and tests excluding the overlapping conditions (Hardiman et al. 2011). However, the etiology of ALS is not fully understood and data show that 90% of ALS cases are sporadic cases (sALS). The other 10% are familial cases (fALS), with a Mendelian mode of inheritance. It suggests that genetic factors may play an important role in ALS (Forbes et al. 2004). However in fALS, more than

20 causative genes have been identified and a number of potential causative or disease-modifying genes that have also been described. It remains therefore challenging to detect pathogenic mutations or risk variants for each ALS individual.

Mavlyutov et al. (2013) first demonstrated that the lifespan of the $SOD1^{G93A}$ mouse model of ALS decreases when crossed with *SIGMAR1* KO mice. In the disease, synaptic coverage of motoneuron (MN) somas by C-terminals remained until death while most other synapses retracted (Pullen and Athanasiou 2009). The σ_1 receptor remains in C-terminals of degenerating MN, suggesting that it could act as a halting factor on increased MN excitability, known as one of the pathological hallmarks of ALS (Pambo-Pambo et al. 2009; Mavlyutov et al. 2013). Administration of σ_1 receptor agonists extended the lifespan of $SOD1^{G93A}$ mice (Mancuso et al. 2012). The σ_1 receptor agonist PRE-084 improved locomotor function and motor neuron survival in presymptomatic and early symptomatic mutant $SOD1^{G93A}$ mice (Mancuso et al. 2012). Peviani et al. (2014) tested the efficacy of PRE-084 in a model of spontaneous MN degeneration, the wobbler mouse. Their results demonstrated that PRE-084, caused an increase of BDNF levels in the gray matter, improved motor neuron survival, ameliorated paw abnormality and grip strength performance, modulated astrocytosis and of macrophage/microglia as part of the mechanisms involved in σ_1 receptor-mediated neuroprotection (Peviani et al. 2014). Another σ_1 receptor agonist, SA4503, has been tested in in vitro and in vivo models of ALS. SA4503 prevented $SOD1^{G93A}$-induced cytotoxicity in NSC34 cells and extended the survival time of $SOD1^{G93A}$ mice (Ono et al. 2014). BD1047, a σ_1 receptor antagonist, blocked the SA4503 cytoprotective effect. Expression of $SOD1^{G93A}$ produced mitochondrial dysfunction in NSC34 cells and associated increase in oxidative and ER stress. The σ_1 receptor agonists have demonstrated antioxidant effects in multiple studies and this mechanism may contribute to the cytoprotective effects of σ_1 agonists in MN cell death and neuroprotection in $SOD1^{G93A}$ mutant mice. SA4503 also upregulates the levels of Akt and ERK1/2. For proliferation and maturation of neural precursors the activation of these pathways plays an important role (Li et al. 2001). MN cells in patients with sALS or fALS and SOD1 mutant mice show decreased levels of phosphorylated Akt (Cheah et al. 2010). Fluvoxamine and dehydroepiandrosterone, acting as σ_1 receptor agonists, also induce phosphorylation of Akt. The σ_1 agonists PRE-084 and 4PPBP induce ERK1/2 phosphorylation in neuronal cells (Maurice and Su 2009; Mavlyutov et al. 2011).

The σ_1 receptor is involved in multiple intracellular pathways in neuronal cells. Immunoelectron microscopy studies showed that σ_1 receptors are localized in subsurface cisternae in C-terminals. Muscarinic type 2 acetylcholine receptors (M2 mAChR), voltage-gated potassium channels (Kv2.1), and small conductance calcium-activated potassium channels (SK) channels are located at C-terminals in the postsynaptic plasma membrane. Subsurface cisternae in postsynaptic densities is believed to correlate with postsynaptic hyperpolarization (Fujimoto et al. 1980; Henkart et al. 1976). It also has been shown that in MN, activation of M2 mAChR inhibits SK channels that reduces after hyperpolarization and as a consequence increases excitability (Mavlyutov et al. 2013). *SIGMAR1* KO mice show higher MN

excitability than their wild-type counterparts, consistent with the notion that the absence of σ_1 receptor prevents activation of Kv2.1 and/or SK channels. The mechanism by which the σ_1 receptor regulates and controls excitation in MN likely involves multiple pathways. In C-terminals, the σ_1 receptor is in close physical proximity to Kv2.1 and SK channels, and their interaction has been observed in several cellular responses (He et al. 2012; Mavlyutov et al. 2010). SK channels are activated by an increase in the concentration of intracellular calcium through N-type Ca^{2+} channels.

Calcium dysregulation and excitotoxicity are the predominant mechanisms associated with pathogenesis in ALS (Grosskreutz et al. 2010; Van Den Bosch et al. 2006). It has, for instance, been reported that blood serum from ALS patients induces abnormal NMDA receptor activation (Texido et al. 2011) and that the excitation/inhibition imbalance in MNs of $SOD1^{G93A}$ mice is due to an increased density of glutamatergic synapses, which could lead to enhanced Ca^{2+} influx into cells (Sunico et al. 2011). Control of NMDA receptor hyperactivation may therefore be an effective approach to preventing MN damage. Indeed, σ_1 receptor agonists have been shown to suppress NMDA currents in rat retinal ganglion cells through a PKC-dependent mechanism (Zhang et al. 2011), to prevent Ca^{2+} dysregulation, and to promote neuroprotection in rat cortical neurons by modulating Ca^{2+} influx through NMDA receptors (Lockhart et al. 1995). Furthermore σ_1 receptor ligands can protect MNs in organotypic cultures against excitotoxicity (Guzman-Lenis et al. 2009) and increase PKC-specific phosphorylation of NR1 subunits in spinal MNs (Mancuso et al. 2012). In the latter study, the authors describe that chronic administration of PRE-084 in $SOD1^{G93A}$ mice from 8 to 16 weeks of age can improve the maintenance of the amplitude of muscle action potentials of MNs and locomotor behavior, and preserve neuromuscular connections and MNs in the spinal cord. PRE-084 also extended survival in both female and male mice by more than 15% (Mancuso et al. 2012). The mechanism of action involved an induction of PKC-specific phosphorylation of the NR1 subunit of the NMDA receptor in $SOD1^{G93A}$ animals and a reduction of microglial reactivity (Mancuso et al. 2012). Agonists of the σ_1 receptor may therefore exert a dual therapeutic action by modulating NMDA receptor-dependent Ca^{2+} influx to protect MNs as well as microglial reactivity to ameliorate the MN environment.

4.4 Multiple Sclerosis

Multiple sclerosis (MS) is a progressive demyelinating disease characterized by disseminated lesions within the nervous system, most likely caused by an autoimmune response to self-antigens (Haghikia et al. 2013). Worldwide, there are an estimated 2.5 million patients suffering from MS, with women twice as frequently affected as men. Pathologically, in the early phase of the disease, perivascular inflammatory infiltrates are observed in the brain, optic nerve, and spinal cord. These infiltrates contain mononuclear immune cells, $CD4^+$ and $CD8^+$ T cells, as well as B cells, monocytes, and macrophages. These infiltrates form plaques, the

end stage of inflammation, characterized by demyelination, astrogliosis, and neuronal as well as axonal degeneration (Compston and Coles 2008; Hohlfeld et al. 2016).

The role of dendritic cells, microglia, and macrophages in the immune invasion of the brain is essential. Dendritic cells present antigen to autoreactive T-cells (Lande et al. 2008; Serafini et al. 2006) and microglial cells trigger the inflammatory response. Experimental autoimmune encephalomyelitis (EAE) induced in mice is a clinically relevant animal model that mimicks several aspects of the disease (Gold et al. 2006; Steinman and Zamvil 2005). Recently, Oxombre et al. (2015) used the EAE model to demonstrate the protective effects of a novel σ_1 receptor agonist, chemically based on a tetrahydroisoquinoline-hydantoin structure. EAE was induced in SJL/J female mice by active immunization with myelin proteolipid protein (PLP) [139–151] peptide. A prophylactic treatment with the compound prevented mononuclear cell accumulation and demyelination in brain and spinal cord and increased T2 B-cells and regulatory T-cells, resulting in an overall reduction in the progression of EAE. The authors concluded that the novel σ_1 receptor agonist decreased the magnitude of inflammation in EAE. The effect was associated with increased proportions of B-cell subsets and regulatory T-cells (Oxombre et al. 2015).

4.5 Huntington's Disease

Huntington's disease (HD) is an autosomal, dominantly inherited neurodegenerative disease, caused by an expansion of cytosine–adenine–guanine (CAG) repeats in the first exon of the huntingtin gene, which encodes the huntingtin (Htt) protein (Dorsey et al. 2013). The inherited mutation results in production of an elongated polyQ mutant huntingtin protein (mHtt). The expansion of CAG repeats leads to the formation of intracellular and intranuclear aggregates in affected neurons (Orr et al. 1993). Patients with HD rapidly develop severe mental and physical disability due to brain atrophy and loss of neurons in the striatum and cerebral cortex (Huntington 1872). No cure or treatment to prevent the progression of HD is currently available. The cellular Htt protein is expressed in most tissues and is involved in protein trafficking, postsynaptic signaling, vesicle transport, transcriptional regulation, and regulation of cell death. Accumulation of the mHtt variant results in alteration of gene transcription, energy production, dysregulation of neurotransmitter metabolism, and activation of intracellular pathways, particularly those leading to ER stress (Reijonen et al. 2008). ER stress and oxidative damage are linked through close communication between the ER and mitochondria. Both play a major role in the neurodegenerative processes in HD (Gil and Rego 2008; Reijonen et al. 2010).

Several recent studies have shown that activation of σ_1 receptor may play a neuroprotective role in HD. First, Hyrskyluoto et al. (2013) showed in an in vitro study using PC6.3 cells overexpressing mHtt that PRE-084 counteracted the toxicity and increased the antioxidative and anti-apoptotic responses of the cells. The cytoprotective effect of PRE-084 involved an upregulation of calpastatin and

induction of the NF-κB pathway (Hyrskyluoto et al. 2013). Second, Miki et al. (2015) showed that accumulation of σ_1 receptor is observed in the nuclear inclusions seen in HD. Using HeLa cells transfected with N-terminal mHtt, they observed that cells harboring mHtt produced σ_1 receptor-positive nuclear inclusions. Small interfering-RNA targeting σ_1 receptor (*SIGMAR1* siRNA) and epoxomicin a specific inhibitor of the proteasome, significantly impaired accumulation of aggregates in the cytoplasm and nucleus. Leptomycin B, a specific inhibitor of exportin 1, also provoked nuclear inclusions. Htt became insoluble after treatments with *SIGMAR1* siRNA and epoxomicin. Proteasome activity increased concurrently along with Htt accumulation but was reduced in *SIGMAR1* siRNA-transfected cells. In contrast, overexpression of σ_1 receptor was associated with decreased number and size of mHtt-containing nuclear inclusions (Miki et al. 2015). However, in this study, the σ_1 receptor agonist PRE-084 and antagonist BD1063 had no effect on cellular viability and proteasome activity. Nevertheless, these findings suggested that in HD the ubiquitin–proteasome pathway is implicated in nuclear inclusion formation, and that the σ_1 receptor participates in the degradation of aberrant proteins in the nucleus via ER-associated degradation machinery.

Third, pridopidine's effect in HD has recently been proposed to involve mainly its agonist action at σ_1 receptors. Pridopidine (4-[3-methanesulfonyl-phenyl]-1-propyl-piperidine), formerly known as ACR16, is a compound from the phenyl-piperidine group of molecules, known as "dopamine stabilizers" or "dopidines" (Pettersson et al. 2010). This class of compounds is being widely investigated in neurodegenerative diseases, including HD (Feigin 2011; Reilmann 2013). Pridopidine is structurally related to 3-(3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP), a racemate whose enantiomers have different effects on dopamine receptors. The (+)3-PPP enantiomer is a weak agonist while the (−)3-PPP enantiomer is a weak antagonist (Mulder et al. 1985). Both drugs have high affinity for the σ_1 receptor, with (+)3-PPP having greater σ_1 receptor binding affinity than (−)3-PPP (Largent et al. 1986a, b; McCann and Su 1991). The structurally related compound (S)-(−)-3-(3-methanesulfonyl-phenyl)-1-propyl-piperidine (OSU6162) binds σ_1 receptors with nanomolar affinity (Sahlholm et al. 2013) and occupies σ_1 receptors rather than dopamine D2 receptors at behaviorally active doses. The authors report a 57% reduction in [^{11}C]SA4503 binding in rats with a dose of 3 mg/kg OSU6162 and 85% inhibition of [^{11}C]SA4503 binding with 15 mg/kg pridopidine, compared to only a 44–66% reduction of [^{11}C]raclopride binding to D2 receptors was observed at 60 mg/kg OSU6162 (Sahlholm et al. 2015). The neuroprotective effect of pridopidine in HD was evaluated using in vivo and in vitro models by Squitieri et al. (2015). These models comprise R6/2 transgenic mice expressing exon 1 of human Htt with approximately 160 CAG repeats and conditionally immortalized mouse striatal knock-in cells expressing endogenous levels of wild-type (STHdh7/7) or mHtt (STHdh111/111). In these models, pridopidine protected cells from apoptosis and improved motor performance and prolonged lifespan in R6/2 mice. The drug enhanced expression of BDNF and DARPP32 in the striatum of the transgenic mice and induced remodelling of mHtt

aggregates. The anti-apoptotic effect was due to enhancement of ERK activation and was blocked by NE100, indicating that the neuroprotective actions of pridopidine are σ_1 receptor-mediated. NE100 alone had no effect on cell survival or signaling in this study. Taken together, these findings support the idea that compounds with affinity for the σ_1 receptor have neuroprotective and disease-modifying properties in HD models and represent potential therapeutic agents for effectively treating the disease.

5 Conclusions

Accumulating evidence supports the notion that selective and non-selective σ_1 receptor ligands may be effective therapeutic agents for neurodegenerative diseases. Inactivation of the σ_1 receptor in animal models exacerbated the pathology and genetic studies suggested that some polymorphisms in the *SIGMAR1* gene could potentiate or appear as risk factors affecting the vulnerability to develop the pathology. These findings are concordant with the notion that σ_1 receptor activity is an important determinant of neuroprotection. Described as a potential *endogenous neuroprotection system* or as a *pluripotent modulator in living system* by some authors (Maurice and Su 2009; Su et al. 2016), the actions of the σ_1 receptor may in fact rely on its association with multiple cellular pathways or at least a complex mode of action. Direct modulation of neurotransmitter activity or second messenger systems, regulation of trophic factors and cytokine activities, modulation of local Ca^{2+} mobilization, preservation of mitochondrial integrity, regulation of transcription factors and gene expression, and activation of ER stress pathways are among the cellular processes affected by σ_1 receptor modulation. The present review has highlighted that PRE-084 is among the most extensively published σ_1 receptor ligands in neurodegenerative disease so far and may serve as a reference compound for future drug discovery and development. It has been reported to be efficacious at 0.3–1 mg/kg doses in models of amnesia, AD, PD, ALS, and HD. Its in vitro and in vivo effects have been described in more than a hundred publications, many of which report comparator data against drugs that are currently in clinical trials, including igmesine, SA4503, and ANAVEX2-73. Finally, a phase II clinical trial is in progress with a σ_1 receptor drug in AD. Other trials may be initiated in the near future and the data generated will be crucial to validate the σ_1 receptor as a drug target in neurodegenerative diseases and better understand the real clinical potential of σ_1 receptor ligands as therapeutic agents in cognitive impairments and neurodegenerative pathologies.

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