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PRE-084 as a tool to uncover potential therapeutic applications for selective sigma-1 receptor activation

Zeinab Y. Motawe, **Salma S. Abdelmaboud**, **Javier Cuevas**, **Jerome W. Breslin**

Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida, Tampa. FL.

Abstract

The discovery of a highly selective putative sigma-1 (σ1) receptor agonist, PRE-084, has revealed the numerous potential uses of this receptor subtype as a therapeutic target. While much work has been devoted to determining the role of σ1 receptors in normal and pathophysiological states in the nervous system, recent work suggests that σ1 receptors may be important for modulating functions of other tissues. These discoveries have provided novel insights into σ1 receptor structure, function, and importance in multiple intracellular signaling mechanisms. These discoveries were made possible by σ1 receptor-selective agonists such as PRE-084. The chemical properties and pharmacological actions of PRE-084 will be reviewed here, along with the expanding list of potential therapeutic applications for selective activation of σ1 receptors.

Keywords

Sigma-1 receptor; neuroprotection; therapeutics; PRE-084; cardioprotection; endothelial protection

Biology of σ1 receptors

The σ receptors were first discovered through pharmacological methods, and were originally classified as an opioid receptor based on behavioral observations by Martin et al., who named it the sigma/opioid receptor[1]. However, Martin also reported that activation of σ receptors by benzomorphan derivatives did not cause analgesia in a manner similar to the parent molecule and classic opioid receptor agonist, morphine. Rather, benzomorphans were found to trigger delusions and psychosis similar to other opioids[1]. Su et al. used the putative σ opioid receptor ligand SKF-10047 to identify a protein that had a nanomolar affinity for SKF- 10047 and no affinity for the opioid antagonist naloxone[2]. The SKF-10047-binding site, as shown by Su, has higher affinity for dextrorotatory benzomorphans like (+)

breslin@usf.edu.

Declaration of interests

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SKF-10047 and (+) pentazocine than for levorotatory isomers, in contrast to opioids that have higher sensitivity to (−) benzomorphans[2]. This finding suggested that the protein identified by Su might not be a true opioid receptor[2]. There was also early confusion about σ receptors and the NMDA receptor's PCP binding site, which is also targeted by (+) SKF-10047[3]. This was later resolved with binding assays using ligands known to be more selective for respective binding sites, such as (+)pentazocine to label σ receptors and TCP to identify PCP-sites. Such studies resolved that σ receptors were indeed not the PCP binding site of the NMDA receptor[4–7].

Two subtypes of σ receptors have been described based upon pharmacological properties, σ1 and σ2. Quiroin et al distinguished between the σ1 and σ2 receptors, reporting that each has distinct functions[8]. They showed that ligands such as pentazocine, carpetapentane and dextromethorphan have high affinity to σ1 receptors and low affinity to σ2 receptors, whereas ligands such as haloperidol and DTG have equal affinity for both subtype[8]. The σ1 receptor, but not σ2 receptor, was also characterized by having phenytoin and GTP sensitivity[8].

The gene that encodes σ1 receptors was first successfully cloned by Hanner et al. in 1996[9]. Since then, the σ1 receptors have gained considerable attention pertaining to their function in cell biology, molecular biology, cancer, immunology, and behavioral neuroscience[10]. On the other hand, σ2 receptors are thought to be involved in cellular processes related to neuropathy[10], as well as cancer biology and have been proposed as a potential drug target in cancer therapy[11]. Moreover, σ2 receptor ligands have been shown to have neuroprotective effects in Alzheimer's disease experimental models[12,13]. In 2017, Alon et al. reported that the gene *TMEM97* encodes the σ2 receptor protein[14].

The σ1 receptor is now known to be a chaperone protein that is ubiquitously expressed and typically located in the endoplasmic reticulum, primarily in the mitochondria-associated ER membranes (MAM)[15]. Encoded by the *SIGMAR1* gene, the σ1 receptor is a non-G-protein-coupled transmembrane protein[16]. Schmidt et al. provided a comprehensive overview of the crystal structure of the human σ1 receptor[17]. Based on their crystallographic description, the structure of the σ1 receptor contains a trimeric organization with one transmembrane domain for each protomer mediated by the carboxy-terminal membrane-adjacent domains[17]. The activity of sigma-1 receptor seems to be dependent on its oligomeric state, which affects and is affected by ligand binding[18]. Moreover, the mono/dimeric state allows its activity as chaperone and high oligomeric states or monomeric are dormant forms of the receptor[19]. Various agonists seem to affect σ1 receptor oligomeric state differently. For example, haloperidol tends to stabilize them in a higher oligomeric state, whereas (+)-pentazocine has the opposite effect of stabilizing lower order oligomers (i.e. the dimers)[18].

The σ1 receptor is ubiquitously expressed in mammals. Hanner et al. were the first to discover the high liver expression of σ1 receptor[9]. In addition, the σ1 receptor has been shown to be expressed abundantly in the intestine, kidney, white pulp of the spleen, adrenal gland, brain, placenta and the lung[20]. Also, nearly all cancer cell lines express the σ1 receptor; with one of the few exceptions being MCF-7 cells[21]. In brain it was reported that σ1 receptors are expressed primarily in cranial nerve nuclei, mesencephalon, red nucleus,

periaqueductal gray matter and substantia nigra, as well as in some diencephalic structures including paraventricular and ventromedial hypothalamic nuclei[20]. While much of the work on the physiological and pathophysiological function of σ1 receptors has focused on the brain, numerous studies have demonstrated that these receptors play an important role in autonomic neuron function[22–24]. More recently, studies have shown very high mRNA levels in vascular tissue and some other tissues that are cataloged in the GTEx portal database (Fig. 1). Bhuiyan et al. have confirmed the expression of σ1 receptors in rat left ventricle[25], while Trujillo et al. have successfully showed its expression in rat lymphatic vessels[26]. More recently, σ1 receptors have been detected in cultured endothelial cells[27].

Langa et al. successfully generated σ1 receptor knockout mice to enable study of the definitive functions of this receptor *in vivo*[28]. Using this model, work by Sabino et al. suggests that σ1 receptors inversely modulate depressive-like behavior in mice[29]. Mice deficient in σ1 receptors displayed increased depressive-like behavior in the forced swim test, with significantly greater immobility behavior than matched wild-type mice[29]. The involvement of σ1 receptors in plasticity and synaptic transmission was evaluated by Snyder et al., who showed that σ1 receptor knockout mice do not have altered neuronal excitability or post synaptic function, but do have reduced long-term potentiation compared to control mice[30]. Moreover, using σ1 receptor knockout mice revealed the importance of this receptor in dentate gyrus neurogenesis, as σ1 receptor knockout mice displayed enhanced proliferation of progenitor cells, a reduction in both survival and neurite outgrowth in newborn neuron, and downregulation of NMDA receptors in these cells[31].

The σ1 receptor has been shown to bind to different molecular partners that play an important role in its effects in different pathologies. For instance, co-immnoprecipitation revealed the binding between σ1 receptor and plasmalemmal potassium and calcium channels which reduced outward potassium current and inhibited L-type calcium channels as well as acid sensing ion channels[22,32,33]. In addition, bimolecular fluorescence complementation assay revealed the binding between σ1 receptor and cannabinoid receptor-1 protein which is involved in NMDAR activity[34]. Moreover, the partnership between NMDAR and σ1 receptor is thought to enhance synaptic plasticity and be neuroprotective in schizophrenia[35].

Chemistry and pharmacology of PRE-084

The non-specific σ receptor ligand, phencyclidine, was used as the parent molecule to develop the highly selective σ1 receptor agonist, PRE-084, by Su et al.[36]. The structure of PRE-084 is reported in Figure 2. This molecule contains the three pharmacophoric moieties for a σ receptor ligand: 1) a hydrophobic cluster, 2) an amine group and 3) an intermediate chain[36]. Conformational analysis showed that PRE-084 matched the pharmacophore models for σ receptor binding with minimal cross reactivity with many other receptors[36]. PRE-084 had an IC_{50} of 44 nM in the sigma receptor assay, an IC_{50} of more than 100,000 nM for PCP receptors and an IC_{50} higher than 10,000 nM in a variety of other receptor systems[36]. The binding between σ1 receptors and PRE-084 was also confirmed by the use of reverse phase liquid chromatography in mouse blood, brain, and spinal cord, which was the first in vivo analysis of PRE-084 binding[37]. The same study showed that PRE-084 was stable in

biological matrices for at least 24 hours[37]. Of note, PRE-084 was shown to promote the dissociation of σ1 immunoglobulin protein (BiP) complex allowing its activity as chaperone[15].

PRE-084 was used in animal models of several CNS pathologies and it was administered in mice in a wide range of doses (from 0.1 to 64.0 mg/kg)[37]. Marra et al studied the pharmacokinetic profile of PRE-084 in comparison of the other σ1 receptor agonist RC-33 in CD1 mice[38]. They injected the mice Intraperitoneally with 10mg/ml PRE-084 and drew blood serially from retro mandibular plexus at 7 time points ending at 8 hours[38]. Using liquid chromatography and mass spectrometry, PRE-084 concentration was measured in different samples. PRE-084 showed a maximal concentration (Cmax) of 659.0 ± 117.1 ng/ml (Tmax of 5 min) with an area under the curve of 45516.4 ± 8386.4 ng/ml*min[38]. The half life of PRE-084 was shown to be 195.517.5 PRE- 084 was shown to be rapidly distributed to CNS showing a concentration in brain, spinal cord and plasma at the Tmax (5 min) of 773.6 ± 26.8 ng/g, 871.5 ± 77.3 ng/g and 651.5 ± 72.6 ng/ml respectively[38].

Despite its characterization as being highly selective for σ1 receptors, there is the potential for off-target effects of PRE-084, which is expected to increase with the dose or concentration applied to the biological system used. In our recent study in which we investigated the role of σ1 receptors in human umbilical vein endothelial cell (HUVEC) monolayer permeability, we found that PRE-084 could elicit enhanced barrier function of the monolayers in a concentration-dependent manner[27]. However, we obtained a particularly interesting finding when we tested the role of σ1 receptors in this model by siRNA-mediated depletion. Under these conditions, we expected that the effect of PRE-084 would be abolished, which is what we observed, but with an additional surprising finding. We found that when PRE- 084 was applied to HUVEC that had significant depletion of σ1 receptors not only was the barrier-enhancing property of PRE-084 abolished as expected, but in addition, PRE-084 actually caused a decrease in monolayer barrier function[27]. This finding suggests that off- target effects of PRE-084 are certainly possible, particularly in this case in which σ1 receptor expression was diminished, allowing for binding to other targets for which PRE-084 may have affinity.

Impacts of PRE-084 on neural tissue:

Activation of σ1 receptors by PRE-084 has been shown to be neuroprotective, and PRE-084 is an enhancer of neurodevelopment in various models. For example, Saulite at al reported that σ1 receptor activation with PRE-084 could facilitate differentiation of skin mesenchymal stem cells to Schwann cells by upregulation of myelin basic protein expression compared to controls[39]. Another study showed that PRE-084 improved neurite elongation of cerebellar granule neurons, probably by TrKB signaling[40]. Neurite elongation by PRE-084 was also linked to protein kinase C (PKC) signaling on motoneurons[41]. These findings support the potential use of σ1 receptor agonists in neurological diseases such as motor and cognitive dysfunction, stroke and other types of brain injury.

PRE-084 and motor function: There are many lines of evidence supporting that PRE-084 is a neuroprotective agent in motor neuron disease models. Spinal muscular

atrophy (SMA) is a motor disease that involves an increase in microglial cell activation. In a mouse mode of SMA, Cervero et al. found that following the application of PRE-084 to SMA mice, the ratio of M1/M2 microglial phenotype was restored, indicating a reduction in microglial activation and concomitant neuroinflammation. There were however some limitations, as PRE-084 did not improve motor neuron atrophy in these mice, and its beneficial effects were not sufficient to decrease motor neuron degeneration[42].

Parkinsonism is a complex neurological disorder involving dysautonomia, sensory deficits and motor impairment[43–45]. In a mouse model of Parkinsonism, PRE-084 significantly improved spontaneous forelimb use. These effects were accompanied by increased density of dopaminergic fibers in the most denervated striatal regions and a modest recovery of dopamine levels. In addition, PRE-084 caused upregulation of neurotrophic factors (BDNF and GDNF) and their downstream effector pathways (extracellular signal regulated kinases 1/2 and Akt)[46].

PRE-084 was also found to be beneficial in an amyotrophic lateral sclerosis model, SOD1-G93A mice (ALS mice)[47]. When PRE-084 was applied in these animals at pre- symptomatic or early symptomatic stages, there was a significant improvement in locomotor function and motoneuron survival[48]. Mancuso et al. further investigated the protective effects of PRE-084 in ALS mice[49]. Their study confirmed the previous finding that PRE-084 improved motor function and motor neuron survival in ALS mice. Additionally, PRE-084 extended survival in both female and male mice by more than 15 %[49]. The mechanisms responsible for these improved outcomes were attributed to induction of protein kinase C-specific phosphorylation of the NR1 subunit of the N-methyl-D-aspartate (NMDA) receptor and a reduction of the microglial reactivity compared with untreated mice[49]. Collectively, these studies suggest the potential therapeutic use of σ1 receptor agonists such as such as PRE-084 in ALS.

Hyrskyluoto et al. have targeted PRE-084 as a therapeutic agent in Huntington disease. Their study showed that PRE-084 could increase cell survival and counteract the deleterious effects of N-terminal mutant huntingtin proteins in neuronal PC6.3 cells. Specifically, PRE-084 increased cellular antioxidants by activating the NF-κB pathway that is compromised by the mutant huntingtin proteins, supporting the future use of σ receptors agonists as therapeutics for Huntington disease[50].

PRE-084 was also used in other motoneuron-injury models. Penas et al. reported that PRE-084 increased GDNF and BiP expression and promoted neuroprotection after root avulsion injury[51]. Furthermore, PRE-084 attenuated head twitch response in mice caused by 2,5-dimethoxy-4-iodoamphetamine[52,53]. However, PRE-084 has not been beneficial in all neurological diseases tested. For example, PRE-084 did not ameliorate seizures in different animal models of this disorder[54,55]

PRE-084 and cognitive disorders: PRE-084 is the σ1 receptor ligand that has been mostly studied in cognitive functions, particularly learning and memory. PRE-084 attenuated amnesia in pharmacological models such as MK-801 induced amnesia[56], amnesia induced

by amyloid beta peptide[57], or hypoxia/ischemia induced amnesia[585960]. Moreover, PRE-084 attenuated amnesia in aged animals[6162].

There is significant evidence supporting the use of σ1 receptor agonists as therapeutics for the treatment of Alzheimer's disease and Alzheimer's-related dementias. PRE-084 attenuated β-amyloid induced cell death[63]. In addition, PRE-084 ameliorated the learning deficits and lipid peroxidation in Alzheimer's disease mouse model[64]. It also decreased tau hyperphosphorylation and amyloid β deposition in a different mouse model[65]. In a non transgenic Alzheimer's disease mouse model generated by amyloid-β 25–35 peptide-injection, PRE-084 protected mitochondrial respiration[66]. This finding suggests potential therapeutic benefits of σ1 receptor activation in Alzheimer's disease especially because mitochondrial dysfunction was shown to be a trigger of Alzheimer's disease pathobiology[67]. In a second study, PRE-084 abolished the inhibitory effect of amyloid-β on long-term potentiation in the pyramidal layer of the CA1 of rat hippocampus[68]. Similarly, PRE-084 attenuated the learning and memory loss in brain ischemia/reperfusion induced vascular dementia model, possibly through NR2A-CaMKIV-TORC1 pathway[60]. An additional σ1 receptor agonist, blarcamesine, has advanced through phase II clinical trials in Alzheimer's disease patients, in which cognitive decline was reported to be reduced[69]. At the time of this writing, blarcamesine is entering phase III clinical trials for Alzheimer's disease.

In addition, σ1 receptor agonism has been shown to alleviate blood-brain barrier dysfunction in a vascular dementia mouse model[70], an effect that suggests σ1 receptors as a therapeutic target for vascular dementia especially because BBB disruption is a key factor in vascular dementia disease pathology[71]. Other cellular effects of PRE-084 that may contribute to improved outcomes in dementia are the promotion of neurite growth in a primary neuronal culture[72] and protection against glutamate induced excitotoxicity in primary hippocampal neurons[73]

Dopamine has been shown to enhance cognition and attention[74,75]. Hong et al. have shown that PRE-084 and other σ1 receptor agonists can facilitate the interaction between σ1 receptor receptors and dopamine receptors, which in turn stabilizes a conformational change in dopamine receptors that facilitates dopamine binding[76] along with enhancement of dopamine levels[77]. In addition to dopamine, NMDA was studied as a target for cognitive enhancement[78]. Some studies provide evidence that PRE-084 also increases the expression of NMDA receptors in rat hippocampus[79,80]. A finding that was consistent with a previous finding of Martina et al. is that σ1 receptor activation potentiates NMDA receptor responses and long-term potentiation by preventing SK currents[81]. PRE-084 rescued the impairment of learning and memory in brain ischemia/reperfusion model by a mechanism involving upregulation of NMDA receptor 2A[60]. These findings further support the potential use of σ1 agonists in cognitive disorders.

Impact of PRE-084 on stroke and brain injury: PRE-084 has been suggested to have neuroprotective effects against excitotoxic brain injury in newborn mice. PRE-084 treatment resulted in a decrease in cell death, as indicated by reduced TUNEL positivity and caspase-3 activation. In addition, there were fewer isolectin B4-positive cells, suggesting a decrease in activated microglial cells[73]. The σ1 receptor agonist PRE-084 reduced infarct volume,

neurological deficits, and pro-inflammatory cytokines while enhancing anti-inflammatory cytokines after embolic stroke in rats[82]. This finding was consistent with the use of other σ receptor agonists in stroke using middle cerebral artery occlusion models in rats[83–85]. PRE-084 was also reported to protect against endoplasmic reticulum stress-mediated apoptosis in mice following cerebral ischemia/reperfusion injury[86]. This was further supported by another study that indicated the possible involvement of NR2A- induced pathway to regulate brain-derived neurotrophic factor[87]. Another stroke study showed that PRE-084 reduced infarct volume, neurological deficits, pro-inflammatory cytokines and enhanced anti-inflammatory cytokines after embolic stroke in rats[82].

Table 1 summarizes some of the applications of PRE-084 in the last few years with the appropriate doses/concentrations that were used. Interestingly, the dose-range of usage of PRE-084 in vivo in mice was very similar across different models.

Cardio-protective actions of PRE-084

Gao et al. have highlighted the important advantage of PRE-084 in cardio-protection. In a rat model of myocardial ischemia/reperfusion, pre-surgical administration of PRE-084 maintained cardiac function and reduced myocardial apoptosis. The proposed mechanism was a reduction of Bax and cleaved−caspase 3 expression associated with increased expression of Bcl−2, and phosphorylation of protein kinase B and endothelial nitric oxide synthase on their activation sites[88]. This observation is consistent with recent findings that σ1 receptor activation with afobazole enhances nitric oxide production in lymphatic endothelial cells, which results in vasorelaxation of rat mesenteric collecting lymphatic vessels[26].

Endothelial barrier-protective actions of PRE-084

In addition to neuroprotection and cardio-protection, our recent study has shown the significance of σ1 receptor activation with PRE-084 in maintenance of endothelial barrier function in cultured HUVEC monolayers. We found that PRE-084 can enhance endothelial barrier function in a concentration- and σ1 receptor-dependent manner[27]. We also observed that PRE-084 enhances endothelial bioenergetics in the form of glycolysis parameters. In addition, PRE-084 could partially counteract endothelial barrier dysfunction caused by the mitochondrial disrupting agent Carbonyl Cyanide Chlorophenylhydrazone (CCCP)[27]. These findings support another recent observation that the σ1 receptor may have protective properties for the blood-brain barrier[70]. Activation of the σ1 receptor is also known to regulate neuroinflammation, specifically astrocytosis and microglial activation, which in turn limits their production of inflammatory cytokines such as IL-1β, IL-10, TNF-α and metalloproteinases. This effect can indirectly impair the blood-brain-barrier[89–92]. Also, given that endothelial barrier disruption and endothelial dysfunction is a main characteristic of many disease models such as stroke[93], myocardial infarction[94], hemorrhagic shock and resuscitation[95] or inflammation[96], our recent findings suggest potential uses of PRE-084 to promote endothelial health in such pathologies.

σ1 receptor agonists in clinical trials

Some σ1 receptor ligands have advanced to clinical trials for various neurological conditions. For example, the σ1 receptor agonist, SA-4503 (cutamesine)[97], has been studied in clinical trials for stroke patients where it was administered starting 48 hours to 72 hours following stroke at the doses of either 1 mg/day or 3 mg/day for 28 days[97]. Cutamesine was proven safe and well tolerated by patients, and the while the drug failed to reach significant effect on functional endpoints, the dose of 3 mg/day improved NIH stroke scale outcomes in patients with greater pretreatment deficits[97]. More research is being conducted on the therapeutic effects of cutamesine in other models such as retinal photoreceptor restoration, cardiac arrest and depression[98–100]. Another σ1 receptor agonist, igmesine, significantly improved depression in a phase II clinical trial[101]. An additional σ1 receptor agonist with mild muscarinic-modulating activity, ANAVEX2–73 (blarcamesine), has been tested in Phase I and II clinical trials in patients with Alzheimer's disease and Parkinson's disease with dementia[69].

The σ agonist, afobazole, went through multiple clinical trials in Russia, and is approved for use in Russia as an anxiolytic agent[102]. Afobazole showed higher tolerability and patient acceptability for the treatment of anxiety in comparison to benzodiazepines[102,103]. Afobazole was tested in patients with generalized anxiety disorders and adjustment disorders[102]. Afobazole caused a significant reduction of Hamilton Anxiety Rating Scale total score that exceeded diazepam[103]. After treatment completion, no withdrawal symptoms were noted in the afobazole group while diazepam withdrawal syndrome was observed in (68%) patients in that study[103]. More potential therapeutic applications and use of σ1 agonists will be highlighted in this review.

Concluding Remarks

Several lines of investigation suggest diverse potential therapeutic uses of σ1 receptor agonists. In this review, we included some of the recent experimental uses of PRE-084 in different disease models. Despite its existence for almost 30 years, PRE-084 is still an important prototypical drug to uncover potential therapeutic benefits of σ1 receptors in central and peripheral diseases. The beneficial effects of σ1 receptor activation include but not limited to enhancement of motor and cognitive functions in neurodegenerative diseases and cardio- protection as summarized in Fig. 3. Most research projects studying σ1 receptor functions to date have been focused on brain and neurological functions. However, σ1 receptor expression levels are high in other tissues. Notably, the σ1 receptor mRNA levels in the liver, blood vessels, bladder, and in cultured fibroblasts have been reported to be higher than in the brain, suggesting new avenues for investigating functional significance of σ1 receptor function in these tissues. The recent finding of expression of σ1 receptors in lymphatic vessels and the connection to endothelial nitric oxide synthase[26,88] as well as the findings that PRE-084 could promote endothelial barrier function[27,70] also suggest the potential use of σ1 receptor agonists for a wider therapeutic utility.

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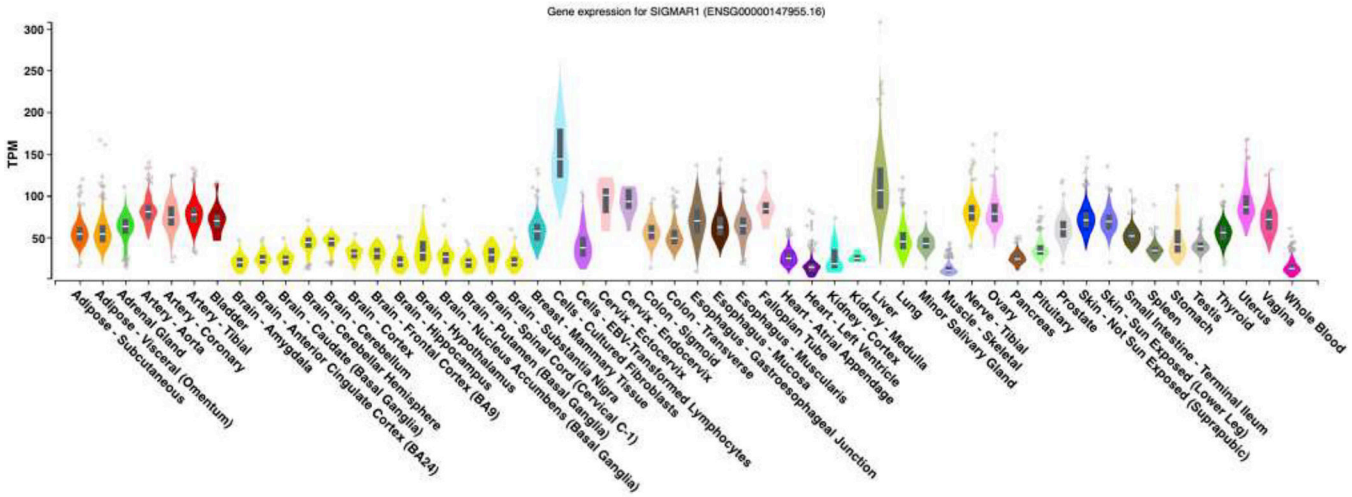

Fig. 1: Gene expression level of σ1 in different human tissues:

Data obtained from GTex portal database, GTEx Analysis Release V8 (dbGaP Accession phs000424.v8.p2). Gene code ID (ENSG00000147955.16), location chr9: 34634722–34637809. Date accessed November 18th, 2019. Gene description: sigma non-opioid intracellular receptor 1 [Source: HGNC Symbol; Acc: HGNC: 8157]. The x-axis shows different tissues tested. The y-axis represents transcripts per million (TPM). Number of examined samples for each tissue ranges from n=4 (kidney: medulla) to n=803 (skeletal muscle).

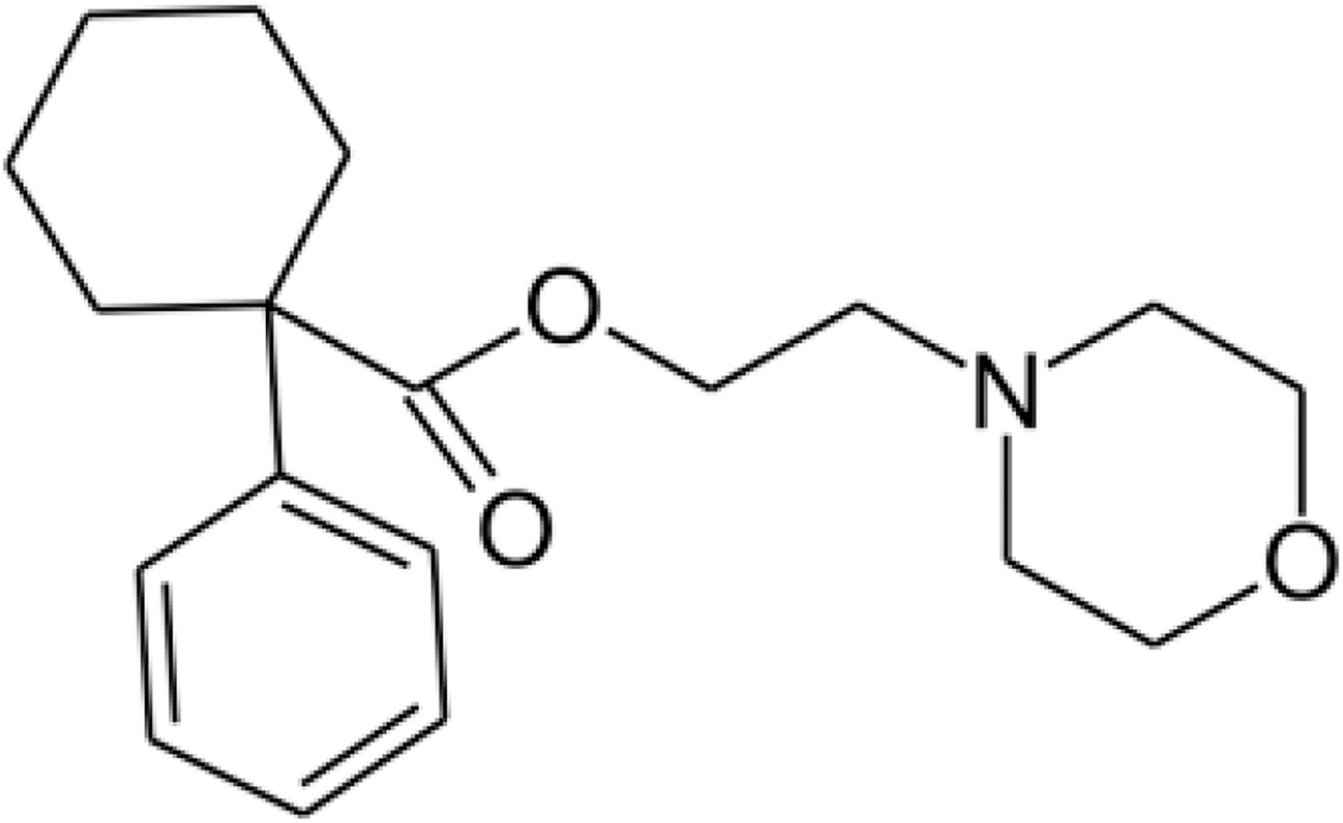

Fig. 2: Chemical Structure of PRE-084:
2-(4-Morpholino) ethyl-1-phenylcyclohexane-1-carboxylate. The active site is the arylcycloalkalyl group, the amine group and the intermediate chain while the phenyl group remains inactive.

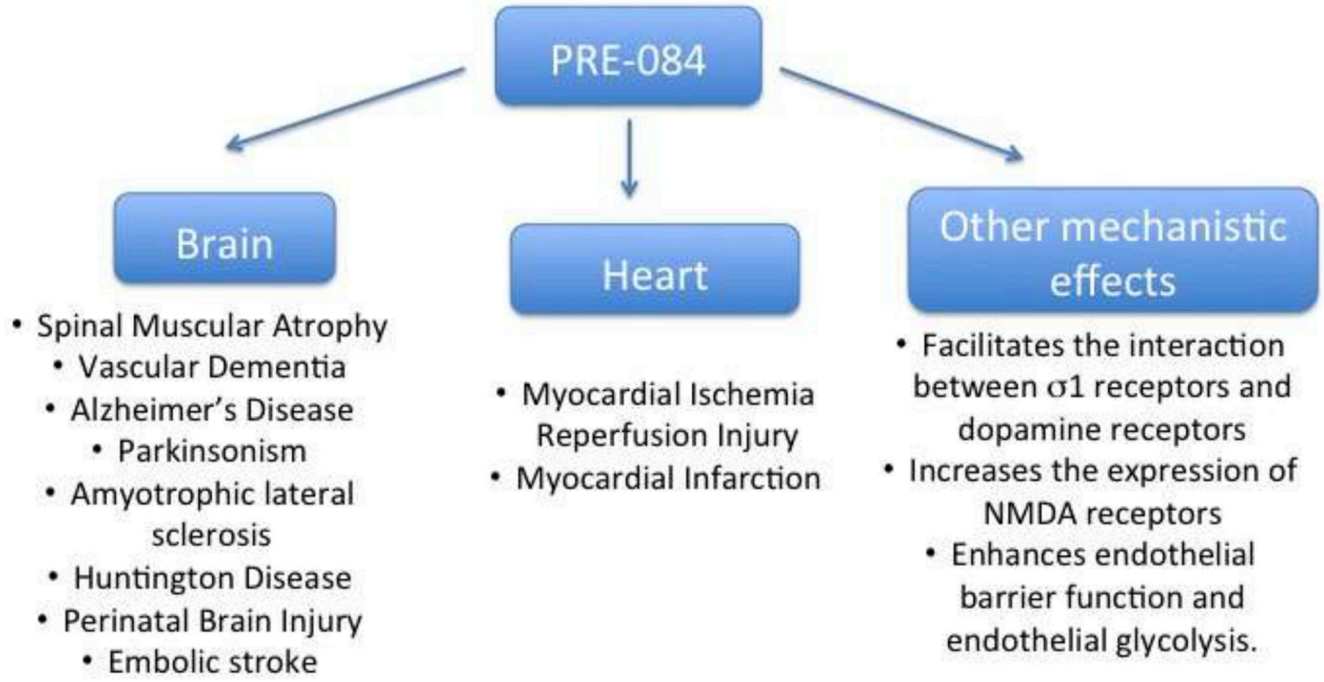

Fig 3.
Summary of uses and applications of PRE-084 in disease models.

Table 1:

Different application an doses/concentrations of PRE-084 in different disease models.

	Application	Organism	Dose	Route of administration	Time of observation of effects	Author
1	Improved NGF-induced neurite outgrowth inhibition by dexamethasone[104]	PC12 cells (rat pheochromocytoma)	1 μM	Added to culture media	24 h	Matsushima, 2019
2	Didn't affect HIV Infectivity[105]	Macrophages	1 μM or 10 μM	Added to culture media	1 h	Omar Vélez Ló pez, 2018
3	Prevent Central Synapse loss in a spinal muscular atrophy mouse model[42]	Mice	0.25 mg/kg/day	Subcutaneous inter-scapular injection	20 days	Clàudia Cerveró, 2018
4	Ameliorates Myocardial Ischemia-Reperfusion Induced Apoptosis[88]	Rats	1 mg/kg	Intraperitoneal injection	1 h	Qi-Jun Gao, 2018
5	Restored synaptic connections between the cortical and striatal neurons in a cell model of Huntington's disease[106]	Corticostriatal culture	100 nM	Added to culture media	1 day	A. V. Bol'shakova, 2017
6	Inhibit catecholamine secretion due to block of nicotinic acetyl choline receptors[107]	Mice adrenal chromaffin cells	5 μM, 10 μM	Added to culture media	20 s	Rebecca L. Brindley, 2017
7	Negative Modulation on N-type Calcium Channel[108]	Rat brain slices	50 μM	Added to bathing solution	100 ms	Kang Zhang, 2017
8	Enhanced differentiation into Schwann cells[39]	Human skin mesenchymal cells	0.3–3 μM, up to 200 μM	Added to culture media	24 hours	L. Saulite, 2017
9	Cytoprotective, attenuated menadione induced DNA damage[109]	Bone marrow	1, 10 μM/ liter	Added to suspension media	30 min	Mikhail V. Voronin, 2016
10	Protects against excitotoxic neonatal brain injury[73]	Mice	0.1 μg/g	Intraperitoneal	1 hour	E Griesmaier, 2012
11	Prevents intracellular calcium dysregulation in cortical neurons during in vitro ischemia[110].	Rat Cortical Neurons	10 or 100 μM	Added to bath solution	2 min	Katnik, 2006