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The Sigma-1 Receptor: Pathophysiological Roles and Therapeutic Potential in Neurodegenerative Diseases

Yasuharu SHINODA, Takayuki NEMOTO, and Takahiro IWAMOTO

Department of Pharmacology, Faculty of Medicine, Fukuoka University

Abstract

The sigma-1 receptor, a chaperone protein mainly localized in the endoplasmic reticulum (ER), regulates cellular calcium homeostasis, stress responses, and neuronal activity. Recent accumulating evidence has indicated that genetic mutations of the sigma-1 receptor are related to neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and distal hereditary motor neuropathy. Preclinical studies have also shown that the activation of the sigma-1 receptor has a beneficial effect on neurodegenerative diseases, such as ALS and Alzheimer's disease, as well as ischemic diseases in the brain and the heart. In this review, we focus on cellular calcium handling by the sigma-1 receptor, and discuss the recent advances in the mechanisms by which the sigma-1 receptor is related to ALS and its role as a potential target in the treatment of neuronal disorders.

Key words: Sigma-1 receptor, Cellular calcium handling, Neurodegenerative disease, Ischemic injury

Introduction

The sigma-1 receptor was first discovered as a binding site of opioid ligand (+)-SKF-10047 (i.e., prototypical sigma-1 agonist) and subsequently identified as a non-opioid receptor according to its pharmacological characteristics[1),2)]. Recent studies revealed that the sigma-1 receptor binds to various proteins, as a chaperone protein that is mainly localized in the endoplasmic reticulum (ER), and functionally modulates cellular calcium homeostasis, stress responses, and neuronal plasticity[3)]. On the other hand, the pharmacological and therapeutic roles of the sigma-1 receptor are intriguing because its ligand binding is a target for various clinical drugs, including selective serotonin reuptake inhibitor (fluvoxamine), antipsychotics (haloperidol) and an anti-Alzheimer's disease (AD) agent (donepezil), as well as (+)-SKF-10047[4),5)].

In this decade, several genetic mutations of the sigma-1 receptor have been identified in patients with neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and distal hereditary motor neuropathy (dHMN), which show the relationship between the loss and/or gain of function and motor neuronal deficits[6)–8)]. Moreover, a previous study reported that mutation (E102Q) of the sigma-1 receptor led to aberrant aggregation and cellular toxicity in NSC-34 cells, a motor neuron-like cell line[9)]. In this review, we discuss the pathophysiological role of the sigma-1 receptor in neurodegenerative diseases, such as ALS and AD, as well as ischemic injury in the brain and heart.

Localization and a Functional Model of the Sigma-1 Receptor

The sigma-1 receptor is a transmembrane protein localized in the ER with 223 amino-acids, which has an N-terminal transmembrane region and a C-terminal chaperone domain[10)–12)]. To date, it has been reported that the sigma-1 receptor interacts with various proteins,

Correspondence to: Takahiro IWAMOTO, Ph.D., Department of Pharmacology, Faculty of Medicine, Fukuoka University 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan.
TEL: +81-92-801-1011 Fax: +81-92-865-4384 E-mail: tiwamoto@fukuoka-u.ac.jp

including inositol-1,4,5-trisphosphate receptor (IP_3R) in the ER, cation channels in the plasma membrane, and nuclear envelope proteins, such as lamin A/C, suggesting that their expression and functions are modulated by these interactions[13]. Two putative functional models of sigma-1 receptor regulation by agonists have been reported[13),14)]. First, the sigma-1 receptor forms a protein complex with another chaperone protein, binding-immunoglobulin protein (BiP) as an inactive state in the quiescent condition, while the sigma-1 receptor agonist elicits dissociation from BiP, translocation and the regulation of the substrate proteins as an active state. Second, sigma-1 receptor forms an inactive homo-oligomer, whereas the agonist upregulates the monomer/dimer, modulating the substrate protein expression or function.

Regulation of Cellular Calcium Handling by the Sigma-1 Receptor

Sigma-1 receptor is considered to regulate cellular calcium handling, stress responses, and neuronal activity through binding with many substrate proteins in several cellular compartments[3]. In particular, it has been well demonstrated that sigma-1 receptor is localized in the mitochondrial-associated ER membrane (MAM), where it is tethered to mitochondria, in which it modulates IP_3R (Fig. 1)[10),15)]. Mitochondrial calcium homeostasis has a pivotal role in cellular processes, like energy production and apoptotic signaling[16),17)]. Sigma-1 receptor regulates calcium transport from the ER to the mitochondria by modulating IP_3R, thereby maintaining cellular energy synthesis[10]. Previous studies reported that this process is affected by dissociation from IP_3R in both a short form of the sigma-1 receptor (a splicing variant lacking the C-terminal chaperone domain) and a mutant associated with ALS (E102Q)[15),18)]. Furthermore, cultured cells expressing the mutant showed a decreased cellular ATP level, which was accompanied by reduced mitochondrial calcium uptake (Fig. 2A, B)[18]. These findings suggest that the sigma-1 receptor is required to regulate IP_3R in MAM and maintain cellular energy production in the mitochondria.

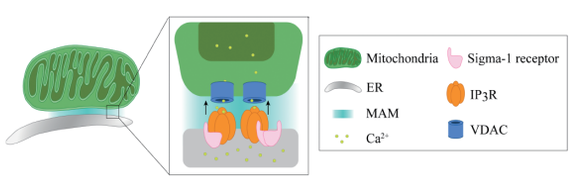

Figure 1. Regulation of calcium release into the mitochondria by the sigma-1 receptor.
(Left) The mitochondria and ER form MAM between the organelles. (Middle) The sigma-1 receptor is localized in the MAM where it regulates IP_3R and calcium ion (Ca^{2+}) transport into the mitochondria via voltage-dependent anion-selective channel protein (VDAC).

Mutations of the Sigma-1 Receptor in Amyotrophic Lateral Sclerosis

Since 2011, genetic mutations of the *SIGMAR1* gene encoding the sigma-1 receptor have been determined in patients with ALS and dHMN[6)–8),19)–24)]. ALS is a progressive neurodegenerative disease characterized by the loss of higher and/or lower motor neurons in the central nervous system. These mutations cause single amino acid substitution or partial C-terminal deletion by frameshift. Moreover, knockout mice with *Sigmar1* gene ablation are reported to show no ALS-like motor deficits[25),26)], suggesting that the gain of function upon mutation is associated with ALS and dHMN. In previous studies, the ALS-related mutant (E102Q) showed dissociation from IP_3R, the depletion of energy synthesis, and increased cell apoptosis, which were consistent with the abnormal aggregation of sigma-1 receptors in NSC-34 cells (Fig. 2A, C)[9),18)]. Prause *et al.* also reported that the sigma-1 receptor is mislocalized in post-mortem motor neurons of sporadic and familial ALS patients[27]. Furthermore, gene ablation of *Sigmar1* aggravates the progression of symptoms in ALS model ($SOD1^{G93A}$) mice, while treatment with sigma-1 receptor agonists delays the deterioration in $SOD1^{G93A}$ mice[28)–30)]. As a new hypothesis derived from these findings, it is inferred that the sigma-1 receptor is associated with motor neuronal survival and that modification by a sigma-1 receptor agonist might be a beneficial strategy for the treatment of ALS.

The Sigma-1 Receptor and Alzheimer's Disease

AD is a neurodegenerative disease with the hallmark of amyloid-β (Aβ) and phosphorylated tau accumulation, in which patients show cognitive decline and memory deficits. In preclinical studies, sigma-1 receptor agonists were shown to regulate toxicity in cells and in a mouse model treated with $Aβ_{25\text{-}35}$[31)–35)]. Sigma-1 receptor agonists (e.g., PRE-084 and afobazole) improved cell viability after the addition of $Aβ_{25\text{-}35}$ in rat primary cultured cortical neurons, suggesting that sigma-1 activation can ameliorate Aβ toxicity[32),35)]. Behensky *et al.* indicated that a sigma-1

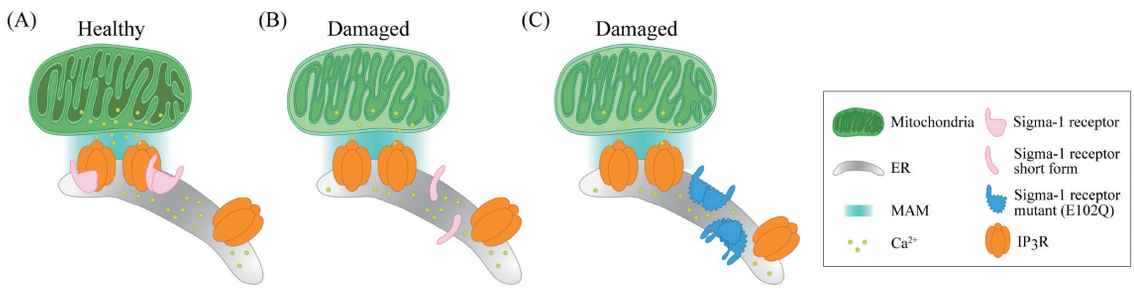

Figure 2. The dissociation of the sigma-1 receptor short form and ALS-related mutant (E102Q) from IP_3R and dysregulated mitochondrial function.
(A) The sigma-1 receptor maintains calcium transport into the mitochondria and mitochondrial ATP synthesis. (B, C) The sigma-1 receptor short form (B), a splicing variant, and ALS-related mutant (E102Q) (C) dissociate from IP_3R, leading to a reduction in the release of calcium into the mitochondria through IP_3R and ATP production.

receptor agonist improved neuronal Ca^{2+} overload and apoptosis, then inhibited Aβ toxicity[35]. In addition, various sigma-1 receptor agonists have been reported to improve cognitive deficits evoked by intracerebroventricular injection of $A\beta_{25\text{-}35}$ in mice[31),33),34)]. This beneficial effect of agonists was abolished by co-treatment with sigma-1 receptor antagonists, suggesting the involvement of the sigma-1 receptor. The mechanism by which sigma-1 receptor agonists improved $A\beta_{25\text{-}35}$ toxicity is considered to involve the inhibition of increased intracellular calcium, reactive oxygen species, and pro-apoptosis signals, although the precise mechanisms still remain unclear.

The Sigma-1 Receptor and Ischemic injury

Cerebral ischemic injury is caused by a transient or permanent decrease in blood flow due to structural or functional alteration of the blood vessels. The mechanism of injury is associated with excitotoxicity, oxidative stress, and inflammation, leading to neuronal loss and disruption of the blood brain barrier[36),37)]. Thus far, in preclinical studies, it has been reported that activation of the sigma-1 receptor has a beneficial effect on ischemic injury in rodents[38)–41)]. These reports suggest that sigma-1 receptor activation can ameliorate excitotoxicity and inflammation, leading to a decrease in the infarct size following ischemia/reperfusion[39),40)]. In addition, recent studies indicated that a sigma-1 receptor agonist abolished blood-brain barrier impairment through the upregulation of proteins (e.g., occludin and claudin-5) that compose the tight junction of brain vascular endothelial cells[42),43)]. However, further study is required to identify the mechanisms by which the activation of sigma-1 receptor improves ischemic injury, including infarction. Moreover, it is also reported that a sigma-1 receptor agonist can abolish cardiac ischemic injury following myocardial infarction[44),45)]. Although the inhibition of endothelial damage after infarction might be involved[45)], it is not completely clear how sigma-1 receptor activation leads to the protection of the damaged heart following ischemia. Taken together, in the future, the sigma-1 receptor could be a therapeutic target for ischemic injury not only in the brain and heart but also in other organs and tissues.

Conclusion

Recent accumulating evidence suggested that the sigma-1 receptor regulates various cellular functions, including calcium transport to the mitochondria and energy production. In this context, we summarized the roles of sigma-1 receptor stimulation in the treatment of neurodegenerative diseases, such as ALS and AD, as well as ischemic insults of the brain and the heart. Future studies are required to elucidate the precise molecular mechanisms for improving these disorders by sigma-1 receptor activation. Based on new insights, targeting the sigma-1 receptor might be beneficial for treating ischemic injury in organs or tissues other than the brain and heart.

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