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Current perspective

# Sigma-1 receptor: The novel intracellular target of neuropsychotherapeutic drugs

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ABSTRACT

Sigma-1 receptor ligands have been long expected to serve as drugs for treatment of human diseases such as neurodegenerative disorders, depression, idiopathic pain, drug abuse, and cancer. Recent research exploring the molecular function of the sigma-1 receptor started unveiling underlying mechanisms of the therapeutic activity of those ligands. Via the molecular chaperone activity, the sigma-1 receptor regulates protein folding/degradation, ER/oxidative stress, and cell survival. The chaperone activity is activated or inhibited by synthetic sigma-1 receptor ligands in an agonist-antagonist manner. Sigma-1 receptors are localized at the endoplasmic reticulum (ER) membranes that are physically associated with the mitochondria (MAM: mitochondria-associated ER membrane). In specific types of neurons (e.g., those at the spinal cord), sigma-1 receptors are also clustered at ER membranes that juxtapose postsynaptic plasma membranes. Recent studies indicate that sigma-1 receptors, partly in sake of its unique subcellular localization, regulate the mitochondria function that involves bioenergetics and free radical generation. The sigma-1 receptor may thus provide an intracellular drug target that enables controlling ER stress and free radical generation under pathological conditions.


## 1. Introduction

In the early 1970s, Martin proposed the sigma receptor as one of the opioid receptor subtypes (i.e., sigma *opioid* receptor), by which the psychotomimetic action of benzomorphans is mediated (1,2). However, following studies had confirmed that the sigma receptor is a non-opioid, non-G protein-coupled, intracellular protein (2,3). Binding assay studies found that the sigma receptor consists of at least two subtypes: sigma-1 and sigma-2 receptor (4). Although the molecular entity and structure were totally unclear until the late 1990s (3), early studies indicated that the sigma-1 receptor may exert therapeutic activities by interacting with several psychoactive drugs, such as haloperidol and selective serotonin uptake inhibitors (SSRIs) (1,5). Further, preclinical studies demonstrated that sigma receptor ligands modulate neuroprotection, cancer growth, ion channel activities, and animal behaviors implicated in memory/cognition, mood, pain, and drug abuse (6–8). Recent advances in molecular biology of the sigma receptor begin elucidating molecular mechanisms by which sigma-1 receptor ligands exert these varieties of actions (2). In this review, firstly molecular pharmacological roles of the sigma-1 receptor are summarized, and then a potential future direction of this research field is discussed.

## 2. Molecular biology of the sigma-1 receptor

From the 1970s to 1990s, hypotheses that tempted to explain the entity of the sigma receptor were proposed: e.g., the opioid receptor subtype hypothesis and the MK801-binding site hypothesis (1,9). However, since radio-ligand binding assays were the only tool to assay the sigma-1 receptor in those days, it was difficult to experimentally and conclusively prove those hypotheses. Therefore, even the existence of the sigma-1 receptor protein was not fully confirmed and accepted. But the debate on the entity of the sigma-1 receptor finally ended in 1996 by the successful cloning of the sigma-1 receptor gene (3). Thanks to the groundbreaking discovery, molecular biological approaches were since then actively introduced to this research field.

The cloning study demonstrated that the sigma-1 receptor consists of 223 amino acids with two potential trans-membrane domains (3). In agreement with the fact that the protein

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possesses a double-arginine ER retention signal at the N-terminus, several recent studies confirmed the ER localization of sigma-1 receptors (10,11). So far, only few electron microscopic data is available that clearly demonstrates the significant plasma membrane localization of the sigma-1 receptor (12,13). The second trans-membrane domain and the C-terminus of the sigma-1 receptor in the ER lumen are proposed to form the ligand-binding site (14). Therefore, in contrast to the majority of ligand-binding sites of neurotransmitter receptors, the binding site of the sigma-1 receptor is located in the inner ER membrane or the lumenal surface of the ER membrane. The unique hydrophobic environment of the ligand-binding site may be enabling hydrophobic molecules to associate with the binding site. Indeed, the most sigma-1 receptor ligands possess hydrophobic or amphipathic property (e.g., haloperidol and fluvoxamine) (1,5). Postulated endogenous ligands of the sigma-1 receptor include steroids (e.g., progesterone, DHEA-sulfate), hallucinogen N,N-dimethyltrypatamine, and sphingosine (15–17). Furthermore, a recent study suggested a possibility that monoglycosylated ceramide might possess a high affinity for the sigma-1 receptor (18). Among sigma-1 receptor-binding lipids, steroids (e.g., progesterone and testosterone, DHEA) seem to have relatively low affinities (0.3–10 μM) when compared with those of endogenous sphingolipids and monoglycosyated ceramides (15,17,18). Certain sphingolipids appear to possess affinities high enough to bind sigma-1 receptors at their physiologically relevant concentrations.

A recent study found that, upon its binding to sigma-1 receptors, the highly selective sigma-1 agonist (+) pentazocine promotes the association of sigma-1 receptors with Insig-1, the SREBP escorting protein localized at the ER (19). Notably, 25-dehydorxylcholesterol exerts the same effect at nM concentrations (19). Though further studies are necessary for confirmation, the data suggests that 25-hydroxycholesterol might serve as a high-affinity endogenous ligand for the sigma-1 receptor.

## 3. The sigma-1 receptor is a novel ligand-operated molecular chaperone (Fig. 1)

The sigma-1 receptor shares no homology with any mammalian protein (3). This fact made it difficult to predict the molecular function of the sigma-1 receptor from the amino acid sequence. Nonetheless, a combination of subcellular localization studies, protein purification studies, coupling proteins identification, and *in vitro* protein activity assays, has begun to reveal the molecular function of the sigma-1 receptor. It was demonstrated that the C-terminus of the sigma-1 receptor possesses a molecular chaperone activity that stabilizes ER proteins, thus being able to regulate their degradation (10,20). The association of another ER chaperone BiP regulates the chaperone activity of the sigma-1 receptor (10). The sigma-1 receptor forming a complex with BiP is in a dormant state, whereas the free sigma-1 receptor that dissociates from BiP exerts maximum chaperone activity (10). The association between sigma-1 receptors and BiP is $Ca^{2+}$-dependent, and thus the depletion of ER $Ca^{2+}$ activates the sigma-1 receptor chaperone (10). Importantly, even in the presence of ER $Ca^{2+}$, sigma-1 receptor agonists cause the dissociation of BiP from sigma-1 receptors, leading to activation of sigma-1 receptor chaperones (10). It was also demonstrated that sigma-1 receptor antagonists inhibit the action of agonists (10). Therefore, synthetic drug that can associate with sigma-1 receptors activate or inhibit the sigma-1 receptor's chaperone activity.

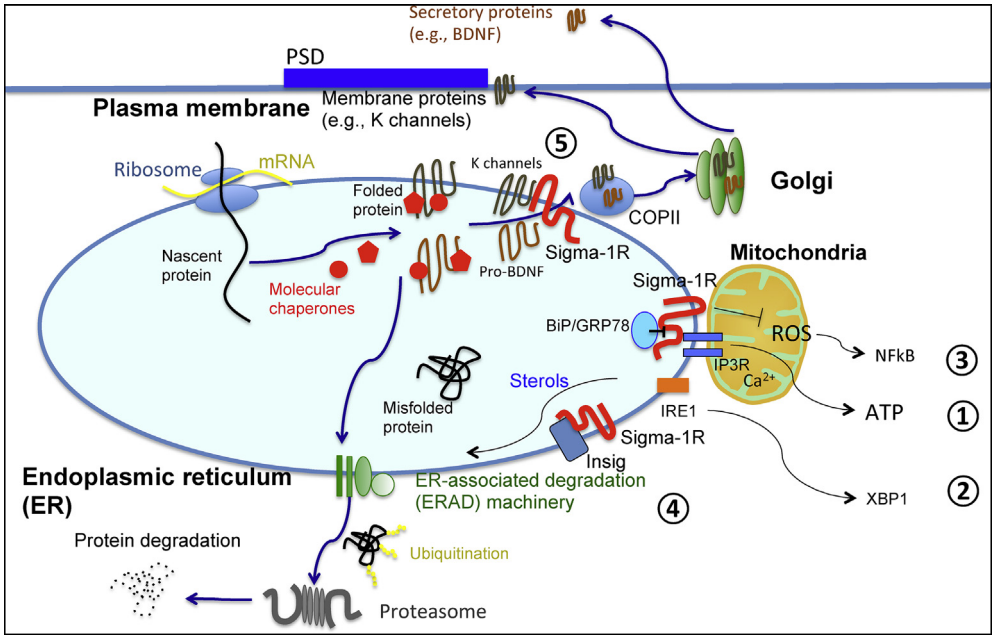


**Fig. 1.** Molecular functions of the sigma-1 receptor. The sigma-1 receptor possesses two transmembrane domains and mainly localize at the ER membrane. Sigma-1 receptors are clustered at the mitochondria-associated ER membrane (MAM) and ER membranes juxtaposing postsynaptic density of specific types of neurons. The ER lumenal domain of the sigma-1 receptor exerts chaperone activities by which ER membrane proteins are stabilized. The figure depicts the recently reported actions of the sigma-1 receptors including: 1) Sigma-1 receptors associating with BiP stabilizes $IP_3$ receptors type-3 (IP3R) at the MAM, leading to regulation of $Ca^{2+}$ influx into mitochondria and following ATP production; 2) Sigma-1 receptors stabilize the ER stress sensor IRE1 at the the MAM in an ROS-dependent manner, leading to prolongation of the IRE1-XBP1 cell survival signal; 3) Sigma-1 receptors suppress generation of reactive oxigen species (ROS) and following activation of the NFkB signaling (How the sigma-1 receptor regulates ROS generation is unknown); 4) Sterols such as 25-hydroxycholesterol promote the association of sigma-1 receptors with Insig-1 [Collaborating with Insig-1, sigma-1 receptors regulate ER-associated degradation (ERAD) of HMG-CoA reductase and galactosylceramide synthase at the ER]; 5) Sigma-1 receptors regulate the trafficking of potassium channel subunits from the ER to the plasma membrane or processing/secretion of brain-derived trophic factor (BDNF). Sigma-1 receptors likely associate with potassium channel subunits or pro-BDNF at the ER. In spinal neurons, sigma-1 receptors, which colocalize with a K channel subunit are clustered at the ER membrane apposing postsynaptic densities (PSD). How the sigma-1 receptor regulates processing/secretion of BDNF is unknown.