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The pharmacology of sigma-1 receptors<sup>☆</sup>Tangui Maurice<sup>a,b,c,\*</sup>, Tsung-Ping Su<sup>d,\*</sup><sup>a</sup> Team II Endogenous Neuroprotection in Neurodegenerative Diseases, INSERM U. 710, 34095 Montpellier Cedex 5, France<sup>b</sup> University of Montpellier II, EPHE, CC 105, Place Eugene Bataillon, 34095 Montpellier Cedex 5, France<sup>c</sup> EPHE, 75017 Paris, France<sup>d</sup> Cellular Pathobiology Section, Cellular Neurobiology Research Branch, IRP, NIDA-NIH, Suite 3304, 333 Cassell Drive, Baltimore, MD 21224, United States

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## ABSTRACT

Originally considered an enigmatic protein, the sigma-1 receptor has recently been identified as a unique ligand-regulated molecular chaperone in the endoplasmic reticulum of cells. This discovery causes us to look back at the many proposed roles of this receptor, even before its molecular function was identified, in many diseases such as methamphetamine or cocaine addiction, amnesia, pain, depression, Alzheimer's disease, stroke, retinal neuroprotection, HIV infection, and cancer. In this review, we examine the reports that have clearly shown an agonist–antagonist relationship regarding sigma-1 receptors in models of those diseases and also review the relatively known mechanisms of action of sigma-1 receptors in an attempt to spur the speculation of readers on how the sigma-1 receptor at the endoplasmic reticulum might relate to so many diseases. We found that the most prominent action of sigma-1 receptors in biological systems including cell lines, primary cultures, and animals is the regulation and modulation of voltage-regulated and ligand-gated ion channels, including Ca<sup>2+</sup>-, K<sup>+</sup>-, Na<sup>+</sup>, Cl<sup>-</sup>, and SK channels, and NMDA and IP3 receptors. We found that the final output of the action of sigma-1 receptor agonists is to inhibit all above-mentioned voltage-gated ion channels, while they potentiate ligand-gated channels. The inhibition or potentiation induced by agonists is blocked by sigma-1 receptor antagonists. Other mechanisms of action of sigma-1 receptors, and to some extent those of sigma-2 receptors, were also considered. We conclude that the sigma-1 and sigma-2 receptors represent potential fruitful targets for therapeutic developments in combating many human diseases.

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**Abbreviations:** AD, Alzheimer's disease; ANAVEX1-41, tetrahydro-N,N-dimethyl-5,5-diphenyl-3-furanmethanamine hydrochloride; BD1047, N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine; CPP, conditioned place preference; DHEA, dehydroepiandrosterone; DTG, 1,3-dio-tolylguanidine; ER, endoplasmic reticulum; Igmesine, (+)N-cyclopropylmethyl-N-methyl-1,4-diphenyl-1-ethyl-but-3-en-1-ylamine hydrochloride; LTP, long-term potentiation; MCAO, middle cerebral artery occlusion; MS-377, (+)-1-(4-chlorophenyl)-3-[4-(2-methoxyethyl)piperazin-1-yl]methyl-2-pyrrolidinone L-tartrate; NMDA, N-methyl-D-aspartate; NE-100, N,N-dipropyl-2-(4-methoxy-3-(2-phenylethoxy)phenyl)-ethylamine hydrochloride; OBX, olfactory bulbectomy; PPBP, 4-phenyl-1-(4-phenylbutyl)-piperidine; PRE-084, 2-(4-morpholinethyl)1-phenylcyclohexanecarboxylate hydrochloride; SA4503, [1-(3,4-dimethoxyphenyl)-4-(3-phenylpropyl)piperazine dihydrochloride; SKF-10047, N-allylnormetazocine.

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## 1. Introduction

The term sigma receptor is derived historically from the sigma/opioid receptor proposed by Martin et al. (1976) to mediate the psychotomimetic action seen with the benzomorphan, N-allylnormetazocine, and its analogs. The receptor was called an opioid receptor because the effect of N-allylnormetazocine was reported to be antagonized by the universal opioid antagonist, naloxone. Attempting to demonstrate the sigma/opioid receptor, Su identified a binding site that, although labeled by the prototypic sigma/opioid receptor ligand ( $\pm$ )SKF-10,047 (( $\pm$ )N-allylnormetazocine), was however insensitive to naloxone (Su, 1982). Mistakenly, the binding site then identified was termed the sigma/opioid receptor (Su, 1982), which in fact is not the sigma/opioid receptor proposed by Martin et al. (1976), as the latter is sensitive to naloxone. It must be mentioned that the SKF-10047 experiment was repeated by the same laboratory at a later date and it was found that the “psychotomimetic” effect caused by SKF-10047 was not blocked by naltrexone, another potent analog of naloxone (Vaupel, 1983; Su et al., 2009). Thus, the name of the binding site identified by Su (1982) was changed to sigma receptor (Su et al., 1988) to differentiate it from the sigma/opioid receptor. The sigma receptor was confused with the PCP/NMDA receptor for a while as some ligands for each receptor cross-react with the other receptor. The confusion was dispelled after it was realized that the confusion arose from the fact that numerous ligands from the two receptors could cross-react. The psychotomimetic effect of SKF-10047 is now believed to be mediated via NMDA receptors, kappa opioid receptors, or sigma-1 receptors (Vaupel, 1983; Su et al., 2009).

Based on the ligand selectivity in the receptor binding assay, as seen in different tissues, the sigma receptor was later found to consist of two subtypes, the sigma-1 and sigma-2 receptors (Hellewell et al., 1994). Apparently, some ligands could bind both subtypes of the receptor. Nevertheless, the sigma receptor identified by Su (1982) is in fact the sigma-1 receptor because the ligand selectivity of the sigma receptor identified by Su (1982), Su et al. (1988) is exactly the same as the sigma-1 receptor demonstrated by Bowen's lab (Hellewell et al., 1994). The exact reason why sigma-2 receptors were not identified in Su's 1982 study could have been that the ligand used in the study did not have sufficient affinity for sigma-2 receptors. The sigma-1 receptor was first cloned in 1996 (Hanner et al., 1996; Seth et al., 1998; Mei & Pasternak, 2001). The sigma-2 receptor has not yet been cloned. This review will focus mainly on the sigma-1 receptor, but will review some data on the sigma-2 receptor as well as it is relevant to the content of the review.

Since the discovery of the sigma-1 receptor, many preclinical studies have implicated the receptor in many diseases. The contents of this review will first examine the role of sigma-1 receptors in different diseases followed by a discussion of potential mechanistic explanations. Because the sigma receptor has been the subject of many excellent reviews in the past, we will focus on discoveries made mainly over the past 10 years.

### 1.1. Addiction

Despite its confusing history in which it was first identified as an opiate receptor subtype and then as a mixed entity with the PCP/NMDA receptor, the sigma-1 receptor has long been known to be involved in addictive processes. Indeed, selective sigma-1 receptor drugs modulate monoaminergic, and particularly dopaminergic and serotonergic, systems. Moreover, an increasing number of recent studies demonstrated that sigma-1 receptor activation plays an important role in plasticity underlying reinforcement and addictive processes (for previous reviews, see Maurice et al., 2002; Matsumoto et al., 2003; Guitart et al., 2004; Maurice & Romieu, 2004).

#### 1.1.1. Methamphetamine

Because methamphetamine binds to sigma-1 receptors, albeit with only moderate affinity (Nguyen et al., 2005), certain actions of meth-

amphetamine are thought to be mediated via sigma-1 receptors. A sigma-1 receptor antagonist, (R)-(+)-1-(4-chlorophenyl)-3-[4-(2-methoxyethyl)piperazin-1-yl]methyl-2-pyrrolidinone-tartrate (MS-377), was indeed found to block the behavioral sensitization caused by methamphetamine in rats (Takahashi et al., 2000). Interestingly, MS-377 did not affect the acute action of methamphetamine, suggesting that the sensitization-blocking effect of MS-377 is not related to attenuation of locomotion, but rather to other unknown mechanism. However, in another report, the acute effect of methamphetamine on locomotion in mice was blocked by the sigma-1 receptor antagonist, N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine (BD1047) (Nguyen et al., 2005). Whether the discrepancy arose from differences in experimental protocols or from differences in species used is unknown. A recent study examined the impact of sigma-1 receptor antagonists, BMY-14802 and BD1047, on stereotypic behaviors induced by methamphetamine in mice (Kitanaka et al., 2008). The drugs differentially modulated the methamphetamine-induced stereotypic responses by, for example, increasing sniffing or decreasing biting. The effect of BMY-14802 was blocked by co-treatment with the agonist, SKF-10047 (Kitanaka et al., 2008). As stereotypic behaviors were purported to be related to psychotomimesis, the latter study might reignite the notion that sigma-1 receptors might bear a relation to psychosis. One of the most interesting studies concerning the involvement of sigma-1 receptors in the action of methamphetamine is a self-administration study. Sigma-1 receptors were found to increase in the midbrains of rats that self-administered methamphetamine in a response-contingent manner, but not in the brains of rats that received the same dose of methamphetamine via passive infusion (Stefanski et al., 2004). The results implicate sigma-1 receptors in the motivational aspect of self-administration, and not in the acute stimulant effect of methamphetamine. However, neither the sigma-1 receptor agonist nor the antagonist, have been examined in methamphetamine self-administration studies.

In a genetic study using the Japanese population, however, sigma-1 receptor polymorphisms, G241T/C240T and A61C, were found to be unrelated to either methamphetamine abuse or the development of methamphetamine psychosis, suggesting that sigma-1 receptor phenotype is not a condition per se for susceptibility to methamphetamine abuse (Inada et al., 2004).

#### 1.1.2. Cocaine

Cocaine binds to sigma-1 receptors with an affinity of about 2 nM (Sharkey et al., 1988) and activates the sigma-1 receptor to induce its stimulant and appetitive properties. Several studies reported that co- or pre-administration of sigma-1 antagonists blocked the hyperlocomotion, sensitization, or the appetitive effect of cocaine using the conditioned place preference paradigm (Romieu et al., 2000, 2002; Matsumoto et al., 2002). All of these behavioral responses were absent in mice repeatedly pretreated with an antisense probe targeting the sigma-1 receptor (Romieu et al., 2000; Matsumoto et al., 2002; Maurice & Romieu, 2004). As neurosteroids also bind sigma-1 receptors (Su et al., 1988), interactions between cocaine and neurosteroids were examined using conditioned place preference (Romieu et al., 2003). The establishment and the expression of the conditioned place preference induced by cocaine were potentiated by the sigma-1 receptor agonists, dehydroepiandrosterone and pregnenolone sulfate. The sigma-1 receptor antagonist, progesterone, blocked the action of the agonist. The results indicate the important role of gonadal hormones and their associated levels in certain individuals with cocaine abuse problems. Further, the sigma-1 receptor agonist, dehydroepiandrosterone, reactivated the conditioned place preference in rats previously conditioned to cocaine in a relapse model (Romieu et al., 2004). The study also found that decreasing sigma-1 receptors via antisense treatment abolished the reactivation of the conditioned place preference, thus firmly establishing the role of sigma-1 receptors in the action of cocaine. In a study linking cocaine to gene regulation, cocaine was found to increase the

level of the immediate early gene, *fos-related antigen 2*, followed by an upregulation of sigma-1 receptors in brain regions that subserve drug abuse (Liu et al., 2005; Liu & Matsumoto, 2008). These data suggest that cocaine regulates the gene expression of sigma-1 receptors via the immediate early gene. Further, by examining cocaine-induced behavioral sensitization coupled with gene and protein expression, the authors observed that cocaine induces the expression of *fra-2*, which leads to a progressive increase in sigma-1 receptor gene and protein expression over a period of days (Liu & Matsumoto, 2008). Thus, the long-term effect of cocaine might be mediated, at least in part, by sigma-1 receptors. The neuronal alterations, if any, associated with the increase of sigma-1 receptors, however, were not presented in the report.

An important experimental procedure in drug abuse research is the drug self-administration paradigm. A recent study examined the effect of the sigma-1 receptor antagonist on the self-administration of cocaine (Martin-Fardon et al., 2007). Cocaine self-administering rats were trained to associate a discriminative stimulus with the availability of cocaine. Rats were then subjected to the reinstatement test following the extinction of cocaine. The sigma-1 receptor antagonist, BD1047, did not block the self-administration of cocaine, but did attenuate the cocaine reinstatement (Martin-Fardon et al., 2007). The results suggested that the sigma-1 receptor antagonist interfered with the processing of reward-related contextual information at the hippocampal level and reduced its motivating impact; an effect that would not interfere with the direct reinforcing actions of drug or natural reward. It is important to note, however, that since BD1047 also blocked cocaine priming-induced reactivation of cocaine CPP (Romieu et al., 2004), an effect thought to be mediated by the nucleus accumbens shell and the ventral tegmental area (Kalivas & McFarland, 2003). Sigma-1 receptors in the nucleus accumbens and the ventral tegmental area may play a role in the reinstatement induced by cocaine priming manipulations (Martin-Fardon et al., 2007).

### 1.1.3. Alcohol

The involvement of sigma-1 receptors in the effect of ethanol was first examined in a study employing the conditioned place preference test (Maurice et al., 2003). The sigma-1 receptor antagonist, BD1047, blocked the ethanol-induced conditioned place preference. The sigma-1 receptor agonist, 2-(4-morpholino)ethyl 1-phenylcyclohexane-1-carboxylate (PRE-084), enhanced the ethanol-induced conditioned place preference in a dose-dependent manner. Although the exact mechanism whereby sigma-1 receptors might relate to ethanol is unknown, results of the study provoke an interesting question: does the sigma-1 receptor serve as a neuronal substrate for CPP in general?

A physiological substratum to the involvement of the sigma-1 receptor in alcohol addiction has been illustrated by Sabeti and Gruol (2008) by investigating the changes in long-term potentiation (LTP) at excitatory CA1 synapses in hippocampal slices from rats exposed to intoxicating concentrations of chronic intermittent ethanol vapors. LTP recorded in early-adolescent ethanol-exposed animals consisted of an NMDA receptor-dependent component and a slow-developing NMDA receptor-independent component. Bath-application of BD1047 and pregnenolone sulfate, but not acute ethanol application, blocked NMDA receptor-independent but not NMDA receptor-dependent LTP (Sabeti & Gruol, 2008). Early adolescent ethanol-exposed animals showed an increased presynaptic function via a sigma-1 receptor-dependent mechanism. By contrast, ethanol exposure after puberty onset in late adolescent animals produced decrements in the level of LTP (Sabeti & Gruol, 2008). In a gene expression study linking sigma-1 receptor polymorphisms to alcoholism, the authors analyzed 307 alcoholic and 302 control subjects and found polymorphisms in the 5'-upstream region: T-485A and TT-241-240 (Miyatake et al., 2004). Using a gene reporter assay, they found that the transcriptional activities of the A-485 and TT-241-240 alleles were significantly reduced. Thus, a higher frequency of those alleles implicates a lower expression of sigma-1

receptors. The frequencies of the A-485 allele and the TT241-240 allele were significantly higher in control subjects when compared with alcoholic subjects. The data, therefore, imply that a lower expression of sigma-1 receptors, supposedly seen in control subjects as implicated by the gene reporter assay, protect those people from alcoholism. The results of this genetic study add support to the notion that sigma-1 receptors are related to the establishment of drug abuse behaviors, such as those seen with methamphetamine and cocaine. Whether sigma-1 receptors might be related to other drugs of abuse remains to be further explored. It must be mentioned, however, that sigma-1 antagonists were able to block the cross-reactivation of cocaine-induced conditioned place preference induced by nicotine, morphine, or phencyclidine (Romieu et al., 2004). Also, a meeting abstract demonstrated the involvement of sigma-1 receptor activation in morphine-induced stimulant and appetitive effects (Maurice et al., 2007). Sigma-1 receptors are also involved in the locomotor stimulant effect of MDMA (Brammer et al., 2006).

### 1.2. Amnesia

Based on the seminal demonstration that sigma-1 receptor agonists potentiated the NMDA-induced neuronal firing in the CA3 region of hippocampus (Monnet et al., 1990) and that sigma-1 agonists increased extracellular acetylcholine levels measured in vivo in the hippocampus or cortex of rats by intracerebral microdialysis (Matsuno et al., 1993), sigma-1 receptors have been extensively studied within the context of learning and memory. Selective sigma-1 agonists failed to improve the learning, consolidation, or retention phases of the mnemonic process when injected alone, but markedly improved the process in animal models of amnesia. Interestingly, a facilitatory effect on memory extinction was seen in mice treated with PRE-084 and submitted to a passive avoidance procedure (Maurice, 2007). Extinction of non-reinforced previous information is a necessary mechanism for adequate learning of new information and, therefore, a promnesic effect of sigma-1 agonist could be seen in particular phases of the mnemonic process. Moreover, in amnesia models induced by the blockade of cholinergic or glutamateric neurotransmissions, or in models via lesional or pathological means, the sigma-1 receptor agonists significantly attenuated the mnemonic deficits as measured by behavioral procedures assessing short-term (working memory), long-term (reference memory), contextual, or spatial memory processes (for extensive reviews, see Maurice & Lockhart, 1997; Maurice et al., 1999, 2001; Guitart et al., 2004; Maurice, 2004, 2007; Monnet & Maurice, 2006).

Numerous sigma-1 receptor agonists were tested in similar mnemonic models, including traditionally recognized sigma-1 receptor ligands such as (+)pentazocine, (+)SKF-10047 (Maurice et al., 1998; Mamiya et al., 2000), more selective compound like PRE-084 (Maurice et al., 2001), igmesine (Earley et al., 1991; Meunier & Maurice, 2004), and SA-4503 (Maurice & Privat, 1997; Zou et al., 2000), or endogenous steroids acting as sigma-1 receptor agonists like dehydroepiandrosterone (DHEA) sulfate (Maurice et al., 1997, 1998; Zou et al., 2000; Maurice et al., 2001; Meunier & Maurice, 2004) and pregnenolone sulfate (Maurice et al., 1998; Zou et al., 2000). In a water-maze test, the impairment of spatial reference memory measured in aged rats could be significantly ameliorated by PRE-084 (Maurice et al., 1994; Maurice, 2001). In addition, compounds which have traditionally been recognized as belonging to other pharmacological classes, but were later identified as sigma-1 receptor ligands, were also examined in the mnemonic test. Thus, dimemorfan, an antitussive agent used for over 25 years, was also found to be a sigma-1 receptor ligand with an affinity of 151 nM (Chou et al., 1999). The drug blocked the amnesic effects induced by scopolamine or  $\beta_{25-35}$ -amyloid peptide treatments in mice submitted to a passive avoidance procedure (Wang et al., 2003). The anti-amnesic action of dimemorfan was blocked by pretreatment with haloperidol, which is known to be a sigma-1 receptor antagonist.

Donepezil (Aricept<sup>®</sup>) is a potent acetylcholinesterase inhibitor that is used in treating Alzheimer's disease. The compound is also a potent sigma-1 receptor ligand with an affinity of 14.6 nM (Kato et al., 1999). A precise pharmacological examination of the interaction of donepezil with the sigma-1 receptor revealed that donepezil is an anti-amnesic agent against dizocilpine-,  $\beta$ -amyloid<sub>25–35</sub> peptide-, or carbon monoxide-induced mnemonic impairment mainly through donepezil's agonistic effect at the sigma-1 receptor (Maurice et al., 2006; Meunier et al., 2006a,b). Tetrahydro-N,N-dimethyl-5,5-diphenyl-3-furanmethanamine hydrochloride (ANAVEX1-41), a potent muscarinic and sigma-1 receptor ligand, was an effective anti-amnesic agent against dizocilpine-induced learning impairments with its effect being blocked by the sigma-1 receptor antagonist, BD1047 (Espallergues et al., 2007). Finally, fluvoxamine, an SSRI with a high affinity at sigma-1 receptors (Iyo et al., 2008), was found to attenuate the cognitive deficit induced by phencyclidine (Hashimoto et al., 2007). Interestingly, fluvoxamine given to a schizophrenic patient also improved the patient's cognitive level in a quite dramatic manner (Iyo et al., 2008).

### 1.3. Pain

The sigma-1 receptor was found to participate in the analgesia mediated by  $\mu$ -,  $\delta$ -,  $\kappa$ 1, and  $\kappa$ 3 opioid receptors (Mei & Pasternak, 2002). This study represents a follow-up study to the group's seminal discovery of the involvement of sigma-1 receptors in opioid analgesia in the 1990s (King et al., 1997). Mei and Pasternak (2002) showed in that 2002 article that the action of sigma-1 receptors in mediating the analgesic action of opioids is mainly supraspinal. In accordance with their earlier reports, the sigma-1 receptor antagonist, haloperidol, potentiates opioid-induced analgesia while the sigma-1 receptor agonist attenuates opioid analgesia. Moreover, the down-regulation of sigma-1 receptors in the supraspinal area potentiates opioid analgesia. Recently, the group has demonstrated that the brain regions important for the action of sigma-1 receptor ligands in modulating morphine-induced analgesia reside in the brainstem, i.e., the periaqueductal gray, the rostroventral medulla, and the locus coeruleus (Mei & Pasternak, 2007). The series of fascinating reports by the group indicate the existence of an endogenous anti-opioid sigma-1 receptor system in the CNS. Their study also provides a tentative molecular explanation, afforded by the haloperidol-sigma-1 receptor interaction, of the long-held mystery of why haloperidol potentiates morphine analgesia which has puzzled medical experts for several decades.

Although results from Pasternak's group have been confirmed by many studies, the exact molecular mechanism whereby sigma-1 receptors affect opioid analgesia is under intensive investigation at present. Using sigma-1 receptor knockout mice, Cendan et al. (2005) showed that formalin-induced pain was reduced in sigma-1 receptor knockout mice. Intrathecal treatment of the sigma-1 receptor antagonist, BD1047, in mice reduced formalin-induced pain and concomitantly attenuated the phosphorylation of N-methyl-D-aspartate (NMDA) receptor subunit 1 induced by formalin (Kim et al., 2006). Further, intrathecal injections of the sigma-1 receptor agonists, PRE-084 and carbetapentane, in mice increased the protein kinase C- and protein kinase A-dependent phosphorylation of the NR1 subunit of the NMDA receptor. The increase was blocked by the sigma-1 receptor antagonist, BD1047 (Kim et al., 2008; Roh et al., 2008a). The same observation was extended to neuropathic pain by the same research group (Roh et al., 2008b). The neurosteroid, DHEA, has been demonstrated to be a sigma-1 receptor agonist by many mnemonic studies (e.g., Maurice et al., 2001). DHEA induced a rapid pronociceptive action in sciatic-neuropathic rats, consistent with it being a sigma-1 receptor agonist (Kibaly et al., 2008). Further, the sigma-1 receptor antagonist, BD1047, blocked the transient pronociceptive effect provoked by DHEA, which is a sigma-1 agonist (Kibaly et al., 2008). Further, Ronsisvalle's group synthesized a new sigma-1 receptor agonist (1R,2S/1S,2R)-2-[4-hydroxy-4-phenylpiperi-

din-1-yl]methyl]-1-(4-methylphenyl)cyclopropanecarboxylate and found that it antagonized kappa opioid receptor-mediated antinociceptive effects (Prezavento et al., 2008).

The exact molecular mechanism of the action of sigma-1 receptors in the modulation of opioid-induced pain and neuropathic pain needs to be definitively established and certainly warrants further investigation.

### 1.4. Depression

Three lines of evidence suggest that sigma-1 receptor agonists can exert an effective antidepressant activity. First, sigma-1 receptor agonists improved cognitive activity in a variety of amnesia models, as they potentiated NMDA or cholinergic neurotransmissions. Secondly, the seminal discovery by Bergeron et al. (1993) demonstrated that antidepressants could behave as sigma-1 agonists in a study in which low doses of the antidepressants sertraline, a selective serotonin reuptake inhibitor (SSRI), and clorgyline, a monoamine oxidase inhibitor, selectively potentiated the effect of NMDA, in a haloperidol-sensitive manner, on pyramidal neurons in the CA3 region of the rat dorsal hippocampus. Thirdly, Narita et al. (1996) reported that SSRI and tricyclic antidepressants showed differential binding affinity to sigma-1 receptors, and in particular demonstrated that fluvoxamine and sertraline have a  $K_i$  value of lower than 100 nM at sigma-1 receptors. This result suggests a role of sigma-1 receptors in the pharmacological action of those drugs. The studies above led to extensive studies targeting sigma-1 receptors for treating depression. Thus, DHEAS, PRE-084, (+)SKF-10,047 (Urani et al., 2001), SA4503 (Skuzza and Rogoz, 2002; Lucas et al., 2008), and 1,3-di-o-tolylguanidine (Skuzza & Rogoz, 2003) were demonstrated to be effective antidepressants in the forced swimming, tail suspension, or conditioned fear stress test. The antidepressant effect of those drugs was blocked by the sigma-1 receptor antagonist, BD1047 (Urani et al., 2001). Dhir and Kulkarni (2008) recently found that the anti-immobility action during forced swimming induced by bupropion, a dopamine uptake inhibitor, was blocked by the sigma-1 receptor antagonists, BD-1047 and progesterone. This last report clearly indicates that the antidepressant-like effect of the clinically used drug, bupropion, is also mediated via sigma-1 receptors, although its binding affinity for the sigma-1 sites has not yet been reported.

The olfactory bulbectomy (OBX) animal model is considered as a highly relevant model for depression since OBX rats exhibit several symptoms representative of the human depressive pathology, including anhedonia (Holmes, 1999). A two-week-long treatment with low doses of igmesine reversed the hyperlocomobility and circling behavior seen in OBX rats (Bermack et al., 2002), suggesting again the efficacy of the sigma-1 receptor compound in the OBX depression model. Igmesine, in particular, has been reported to be an effective antidepressant in the forced swimming test (Urani et al., 2001), the tail suspension test (Ukai et al., 1998), the conditioned fear stress test (Urani et al., 2004), and in the OBX model (Bermack et al., 2002). The drug was studied at the clinical level in a double-blind, large-scale trial carried out in the U.K. and Eastern Europe (Pande et al., 1999; Volz & Stoll, 2004). Four groups were studied (placebo, 25 or 100 mg/day igmesine, and 20 mg/day fluoxetine as a positive control) and patients were scored using the total Hamilton depression rating scale (HAMD). The global response was negative, partly due to a high response rate of the placebo group. When considering the inpatient subgroup, however, it was found that both the igmesine (25 mg/kg) and fluoxetine groups showed a statistically significant effect superior to placebo, thus confirming the sigma-1 drug as a clinically effective antidepressant. Its development was, however, finally discontinued due to marketing considerations (Pande et al., 1999; Volz & Stoll, 2004). Interestingly, in two Alzheimer's disease-related depression models, i.e., in mice treated i.c.v. with amyloid  $\beta_{25–35}$  peptide and then subjected to forced swimming or in rats infused i.c.v. with amyloid  $\beta_{1–40}$  protein and subjected to conditioned fear stress, (+)SKF-10,047, PRE-084, igmesine and/or DHEA sulfate were more effective

than controls in alleviating depressive-like symptoms (Urani et al., 2002, 2004). In contrast, SSRI or tricyclic antidepressants appeared equally or less effective, suggesting a great potential for sigma-1 receptor agonists in treating depressions often observed in Alzheimer's patients that are resistant to the currently available treatments. All previous studies examining the antidepressant action of sigma-1 receptors utilized sigma-1 receptor ligands to activate the receptor and then examined the involvement of sigma-1 receptors in depression. A recent study, however, utilized sigma-1 receptor knockout mice and examined the depressive-like phenotype in those mice (Sabino et al., 2009). The sigma-1 receptor knockout mice exhibited normal anxiety-like behavior and normal locomotor activity, but showed increased immobility in the forced swimming test. The results of this study indicate that sigma-1 receptors themselves, or perhaps in corroboration with endogenous ligands, are related to the depressive-like behavior.

The physiological substratum has been extensively studied by Debonnel and collaborators. They reported in a series of electrophysiological studies that selective sigma-1 agonists (including igmesine, DTG, (+)SKF-10,047), non-selective sigma-1 ligands acting also as 5-HT ligands (OPC-14523), antidepressants (sertraline or cloglyline), or neurosteroids acting also as sigma-1 agonists (DHEA and DHEA sulfate) all modulated the firing activity of both 5-HT neurons in the dorsal raphe nucleus and glutamatergic neurons in the hippocampus; both structures being important in depression pathophysiology (Bermack & Debonnel, 2001, 2005a,b, 2007; Bermack et al., 2004; Robichaud & Debonnel, 2004). Debonnel and colleagues specifically demonstrated that sigma-1 ligands have potential as antidepressants with a fast onset of action, as they produce a rapid modulation of the 5-HT system in the dorsal raphe nucleus and glutamatergic neurotransmission in the hippocampus.

### 1.5. Alzheimer's disease

As mentioned earlier, the efficacy of sigma-1 receptor ligands as anti-amnesic or antidepressant drugs was tested in Alzheimer's disease (AD)-relevant models of amnesia. Relevant nontransgenic models of AD have also been characterized in rats infused with the amyloid  $\beta_{1-40}$  protein or in mice injected centrally with amyloid  $\beta_{25-35}$  peptide (Yamada & Nabeshima, 2000). Selective sigma-1 compounds, like (+)-pentazocine, PRE-084, or SA4503 attenuated, in a dose-dependent and bell-shaped manner, the memory deficits observed in mice seven days after  $\beta_{25-35}$  peptide injection (Maurice et al., 1998). This effect was shared by non-selective sigma-1 receptor compounds, including the cholinesterase inhibitor, donepezil (Meunier et al., 2006b) or the muscarinic ligand, ANAVEX1-41 (Villard et al., 2009) that, nevertheless, mediate their effects through sigma-1 receptors. However, the first evidence that sigma-1 receptor ligands could show some neuroprotective activity against amyloid toxicity arose from an *in vitro* study by Marrazzo et al. (2005). In cultured cortical neurons,  $\beta_{25-35}$  peptide-induced neuronal death was blocked by PRE-084 or methyl (1S,2R)-2-[1-adamantyl(methyl)amino]methyl-1-phenylcyclopropanecarboxylate ((-)-MR-22). The neuroprotective effects of the compounds were, in turn, blocked by the sigma-1 receptor antagonist, NE-100 (Marrazzo et al., 2005). Taken together, these results suggested that sigma-1 receptor agonists might be useful agents in treating AD because they could not only alleviate the cognitive deficits observed in AD patients, but may also reduce neuronal damage. The *in vivo* preclinical confirmation of this hypothesis came from studies by Meunier et al. (2006b) and Villard et al. (2009). When the selective sigma-1 compound, PRE-084, or the non-selective compounds which act also as sigma-1 agonists, namely donepezil or ANAVEX1-41, were co-injected with  $\beta_{25-35}$  peptide into mice, these drugs blocked the  $\beta_{25-35}$  peptide-induced toxicity in the hippocampus and also attenuated the learning and memory deficits in mice. In fact, those drugs were able to attenuate the cell loss observed in the CA1 pyramidal neuron

layer of the hippocampus, the astroglial reaction measured by increase in GFAP immunolabeling in the cortex and hippocampal hilus, the induction of oxidative stress measured by increase in lipid peroxidation or protein nitration in the hippocampus, the induction of the expression of caspase-12, a marker of the endoplasmic reticulum stress, or caspase-3, a marker of apoptotic processes (Meunier et al., 2006b; Villard et al., 2009).

It is worth mentioning that in a human positron emission tomography (PET) study employing [ $^{11}\text{C}$ ]SA4503, a lower density of sigma-1 receptors was found in early Alzheimer's patients compared to age-matched controls (Mishina et al., 2008). This study confirmed the previous *ex vivo* data (Jansen et al., 1993), but the validity of the data and the interpretation of it must be taken with caution because three out of five AD patients in the study were treated with donepezil, which is known to interact with sigma-1 receptors (Kato et al., 1999; Maurice et al., 2006; Meunier et al., 2006a,b). The gene variation study with the sigma-1 receptor has produced surprising results. There are two common genetic variations identified in the sigma-1 receptors: G241T/-C240T and A61C. In the Japanese population, a study reported that the TT-C haplotype, implying a lower expression of sigma-1 receptors, was a protective factor for AD (Uchida et al., 2005). This result suggests that lower sigma-1 receptor levels, even though activation of sigma-1 receptors is neuroprotective, are good for the AD. However, in another study examining AD in the Polish population, the authors reported no significant differences in the sigma-1 receptor alleles between the diseased and the control groups (Maruszak et al., 2007). The exact reason for the discrepancy is unknown at present.

### 1.6. Schizophrenia

Although the traditional antipsychotic, haloperidol, binds to sigma-1 receptors with high affinity (Su et al., 1988), the involvement of sigma-1 receptors in schizophrenia has not been clearly demonstrated. In an open label study examining the efficacy and safety of a sigma-1 receptor ligand, EMD 57455 (panamesine), the intent-to-treat analysis showed significant improvement in the psychometric variables assessed by several scales (Huber et al., 1999). No follow-up information is available at present, and the exact biochemical mechanism, if any, that might relate sigma-1 receptors to schizophrenia has not yet been established.

The study of the association between polymorphisms in sigma-1 receptor gene and schizophrenia has produced conflicting results. One study reported polymorphisms at two regions (GC-241-240TT and Gln2Pro) and showed a significant association between the TT/Pro2 haplotype and schizophrenia (Ishiguro et al., 1998). Two other studies have since confirmed the polymorphisms, but found no association of the gene variations with schizophrenia (Ohmori et al., 2000; Uchida et al., 2003). Another study has identified yet two more polymorphisms of sigma-1 receptor genes in the 5'-upstream region (T-485A and G620A), but could not find an association to schizophrenia (Satoh et al., 2004). The exact reason for the discrepancies between those reports has not been identified. Thus, the questions of whether sigma-1 receptors confer susceptibility to schizophrenia or are related to schizophrenia in any way are not yet clarified.

### 1.7. Stroke

A potent sigma-1 receptor agonist, 4-phenyl-1-(4-phenylbutyl)-piperidine (PPBP), was examined for neuroprotective properties in rats by using the middle cerebral artery occlusion (MCAO) with the intraluminal suture occlusion technique (Harukuni et al., 2000). Sixty minutes after the onset of ischemia, the PPBP was infused (*i.v.*) for 24 h. PPBP significantly reduced the infarction volume in the cortex (Harukuni et al., 2000). The neuroprotective property of PPBP correlated with the attenuation of nitric oxide production, and the anti-ischemic property of PPBP was mimicked by a nitric oxide synthase inhibitor

(Goyagi et al., 2001). As the accumulation of extracellular dopamine is detrimental to neurons, the same research group examined the concentration of dopamine in PPBP-treated rats and found that the action of PPBP has nothing to do with dopamine (Goyagi et al., 2003). To further examine the involvement of nitric oxide synthase in the neuroprotective action of sigma-1 receptors, Vagnerova et al. (2006) used inducible nitric oxide synthase knockout mice. Results showed that although (+)pentazocine was neuroprotective in wild type mice, it provided no additional neuroprotective benefit to the knockout animals, suggesting that sigma-1 receptor agonists might cause neuroprotection by suppressing cell death related to toxicity generated by nitric oxide synthase. In yet another study, Yang et al. (2007) used cultured cortical neurons and exposed them to oxygen-glucose deprivation or glutamate, and found that the neuroprotective action of PPBP was related to the preservation of the anti-apoptotic protein, Bcl-2.

The most dramatic result showing the effect of sigma-1 receptor ligands in neuroprotection came from a study by using a non-selective sigma-1/sigma-2 ligand 1,3-di-o-tolylguanidine (DTG). Ajmo et al. (2006) demonstrated that 24 h after the MCAO in rats, a subcutaneous injection of 15 mg/kg of DTG significantly reduced infarct areas in both cortical/striatal and cortical/hippocampal regions by >80% relative to control rats. The efficacy of DTG was due to cell survival, but also due to a reduction of the inflammatory response in the brain (Ajmo et al., 2006). The same research group further showed that the effect of DTG was due to its ability to reduce the intracellular calcium concentration caused by ischemia and that this calcium effect of DTG was blocked by the selective sigma-1 receptor antagonist, BD1047 (Katnik et al., 2006). Thus, it appears that DTG might exert its neuroprotective effects via sigma-1 receptors as a sigma-1 receptor agonist. However, the possible involvement of sigma-2 receptors in the anti-ischemic effect of DTG cannot be totally excluded at present because BD1047 has appreciable affinity at sigma-2 receptors.

Other sigma-1 receptor ligands have also been shown to be neuroprotective. The antitussive agent and sigma-1 receptor ligand, dimemorphan, was found to be neuroprotective in MCAO rats (Shen et al., 2008). The selective sigma-1 receptor agonist, PRE-084, was also included in that study. Dimemorphan and PRE-084 ameliorated the size of infarct zone by 70% and 50%, respectively, and the protective effects were blocked by BD1047 (Shen et al., 2008). The neurosteroid sigma-1 receptor ligand, DHEA, was shown to provide robust neuroprotection in rats after transient global ischemia and the protective effect of DHEA was blocked by the sigma-1 receptor antagonist, NE100 (Li et al., 2006, 2009). In a brain slice preparation examining the effect of drugs on spreading depression, a profound but transient depolarization of neurons and glia that migrates across cortical and subcortical gray during ischemia, Anderson and Andrew (2002) found that pretreatment with the sigma-1 receptor agonists, dextromethorphan or carbetapentane, significantly blocked the spreading depression cause by exposing slices to potassium chloride. Although dextromethorphan and carbetapentane have an appreciable affinity for other receptors, the blockade of the spreading depression by those two drugs was removed by treatment with the sigma-1 receptor antagonist, 1-[2-(3,4-dichlorophenyl)ethyl]4-methylpiperazine (BD1063) (Anderson & Andrew, 2002).

### 1.8. Retinal neural degeneration

The existence of sigma-1 receptors was unequivocally demonstrated in neural retinas, particularly in the ganglion cells which are most susceptible to excitatory degeneration (Ola et al., 2001). In addition to studies in which sigma-1 receptor ligands have been shown to be active neuroprotectants in the brain, many studies have demonstrated the efficacy of sigma-1 receptor ligands in the protection of retinal neurons. Martin et al. (2004) showed that the sigma-1 receptor agonist, (+)pentazocine, prevented apoptotic retinal ganglion cell death induced by glutamate. By using the newly synthesized sigma-1 receptor ligand N-methyladamantan-1-amine derivative (-)

MR22, Bucolo et al. (2006) demonstrated that the compound protected rat retinas against ischemic damage by abrogating the decrease of glucose and ATP when compared to the control. Later, Bucolo and Drago (2007) demonstrated that neurosteroid sigma-1 receptor ligands also protected retinal tissues. As  $\beta$ -amyloid is toxic to the retina, the sigma-1 receptor agonist, PRE-084, was used to examine if it might protect retinas against  $\beta$ -amyloid-induced retinal degeneration. Indeed, PRE-084 was protective in retinal neurons and was effective in abrogating the  $\beta$ -amyloid-induced biochemical changes, including the overexpression of TRAIL and the apoptotic protein, Bax, and the phosphorylation of JNK (Cantarella et al., 2007). Further, the effect of PRE-084 was blocked by BD1047 (Cantarella et al., 2007). Another laboratory used primary ganglion cells isolated from rat retinas and found that (+)pentazocine prevented the excitotoxicity to cells (Dun et al., 2007). The same laboratory extended their finding to an in vivo model of retinal neurodegeneration (Smith et al., 2008). The downstream mechanism underlying the retinal neurodegeneration was examined in cultured retinal ganglion cells. Thus, Tchedre and Yorio (2008) found that (+)SKF-10047, a sigma-1 receptor agonist, inhibited the increase of apoptotic protein Bax and the activation of caspase-3 in glutamate-exposed retinas, suggesting the blunting of death signaling in the sigma-1 receptor ligand-treated retinal ganglion cells. Those findings might, by extension, implicate sigma-1 receptors in the etiology of diabetic retinopathy.

The involvement of sigma-1 receptors in the survival of human lens cells was examined in a couple of studies. The existence of sigma-1 receptors was first confirmed in human lens cells, and subsequent studies used either the sigma-1 receptor antagonist, BD-1047, or the silencing of sigma-1 receptors to demonstrate the role of sigma-1 receptors. BD-1047 inhibited human lens cell growth (Wang et al., 2005). The siRNAs against sigma-1 receptors caused a reduction of lens cell growth and a concomitant decrease of ERK and Akt phosphorylation induced by thrombin (Wang & Duncan, 2006).

### 1.9. HIV and immunity

Because cocaine binds to sigma-1 receptors and because cocaine leads to enhanced HIV replication, the role of sigma-1 receptors in cocaine-induced immune alteration and HIV expression was examined in several studies. Using human peripheral blood mononuclear cells implanted into severe combined immunodeficiency mice, Roth et al. (2005) showed that activation of those cells in vitro by cocaine increased the expression of the CC chemokine receptor 5 and CXC chemokine receptor 4 coreceptors. These effects preceded the boost in HIV infection, and the increased viral infection caused by cocaine was blocked by the sigma-1 receptor antagonist, BD-1047 (Roth et al., 2005).

The role of neuroimmunopharmacological involvement of sigma-1 receptors in phagocytes, such as microglial cells, was examined in a study employing microglial cell culture (Gekker et al., 2006). Treatment of microglial cells with cocaine resulted in a concentration-dependent increase in HIV expression, as assessed from the culture supernatant. Further, the cocaine-stimulated increase of HIV expression was blocked by BD-1047, a sigma-1 receptor antagonist (Gekker et al., 2006). The underlying mechanism of these fascinating observations certainly warrants further investigation.

### 1.10. Cancer

The study of sigma-1 receptors and associated ligands in cancer or tumors represents a relatively new area of cancer research. The discovery of the presence of sigma-1 and sigma-2 receptors in many human and rodent cell lines opens up this new area of cancer research (Wojciech et al., 1991; Vilner et al., 1995). By testing a range of tumor cell lines, Spruce et al. (2004) showed that sigma-1 receptor antagonists, including rimcazole, reduced haloperidol, BD-1047, and BD1063, all evoked a concentration- and time-dependent decline in cell viability in tumor

cells. It is known, however, that haloperidol, rimcazole, and BD-1047 are not very selective sigma-1 receptor ligands. Further, the sigma-1 receptor agonists, (+)SKF-10047 and (+)pentazocine, abolished the suppressant effect of the antagonist (Spruce et al., 2004). Upon examining human neoplastic breast epithelial cells and cell lines, Wang et al. (2004) found that sigma-1 receptors were expressed in those cells and that the sigma-1 receptor antagonists, haloperidol, reduced haloperidol, and progesterone produced a dose-dependent inhibition of the growth of those cells at high concentrations. Interestingly, because sigma-1 receptors are expressed at a higher level in breast cancer cells and because haloperidol is a potent sigma-1 receptor ligand, a study designed “haloperidol-associated stealth liposomes” as “bullets” to deliver target genes to cancer cells. The study showed that the haloperidol-conjugated liposomes produced the transgene at 10-fold higher levels than control liposomes (Mukherjee et al., 2005).

In lieu of detecting sigma-1 receptors via a receptor binding assay, a recent study confirmed the overexpression of sigma-1 receptors in cancer cells first by using real-time PCR to confirm the mRNA level and then by using a selective sigma-1 receptor antibody to detect the protein (Aydar et al., 2006). The study found that human breast cancer cell lines expressed significantly higher levels of sigma-1 receptors and that silencing sigma-1 receptors by siRNA significantly reduced the cancer cell line's proliferation when compared to that of control cells. Using a newly synthesized sigma-1 receptor ligand, 4-(N-benzylpiperidine-4-yl)-4-iodobenzamide, Megalizzi et al. (2007) found that the drug decreased the growth of human A549 NSCLC and PC3 prostate cancer cells in a dose-dependent manner and markedly decreased the expression of proteins involved in drug resistance, including glucosylceramide synthase.

An interesting twist linking sigma-1 receptors to cancer came from studies examining the effect of sigma-1 receptor agonists like cocaine on lung cancers. Two studies (Zhu et al., 2003; Gardner et al., 2004) found that sigma-1 receptor agonists, including cocaine and PRE-084 promoted tumor growth, in an IL-10-dependent manner, and that this effect of sigma-1 receptor agonists was blocked by either the sigma-1 receptor antagonist or the antibody against IL-10. Thus, it appears that the activation of sigma-1 receptors promotes tumor growth. However, Simony-Lafontaine et al. (2000) examined sigma-1 receptors immunocytochemically in 95 human breast cancer patients and found no statistically significant relationship between sigma-1 receptors and tumor size or histologic grade. Further, the study found a surprising correlation contrary to the common notion that sigma-1 receptors promote tumor growth, and showed that the higher the sigma-1 receptor level, the longer the patients live as disease-free survivors (Simony-Lafontaine et al., 2000). At present, it is difficult to reconcile this paradoxical finding with other findings predominantly indicating that sigma-1 receptors promote cancer growth.

Although this review mainly focuses on sigma-1 receptors, it has to be mentioned that the research on cancer is the most active area for sigma-2 receptors. Thus, some important reports relating sigma-2 receptors to cancer will be mentioned here. Pioneered by the discovery from Bowen's lab, sigma-2 receptor agonists have been found to mediate a novel caspase-independent apoptotic pathway involving ceramide in several breast tumor cell lines (Crawford and Bowen, 2002; Crawford et al., 2002, 2003). Using immortalized and transformed cells of various origins, Ostensfeld et al. (2005) found that a new sigma-2 receptor ligand, siramesine, caused tumor cell death. However, siramesine did so via a caspase-independent mechanism (Ostensfeld et al., 2005). The action of siramesine was later identified to be related to lysosomes and autophagosomes (Ostensfeld et al., 2008). High doses of haloperidol were also found to cause cell death in PC12 preneuronal and N2a neuroblastoma cells via a sigma-2 receptor-mediated mechanism involving Bcl-XS (Wei et al., 2006).

The mechanisms of action of sigma-1 receptors and sigma-2 receptors involved in cancer biology will be discussed further in the next section.

## 2. Mechanistic considerations

How can an ER protein be related to so many diseases, at least as indicated by cellular or preclinical disease models? It seems quite convincing that the sigma-1 receptor is related to the diseases discussed here because the involvement of sigma-1 receptors has been demonstrated by the molecular biological silencing of the receptor, and thus proven except in the case of schizophrenia and HIV infection. As for sigma-2 receptors, the selectivity as indicated by binding assays also attests to the specific involvement of the receptor in the death signaling of cancer cells. Inasmuch as the sigma-1 receptor is well established in its sequence and subcellular localization, we ask one very simple question: what is the function of this dynamic ER-resident protein called sigma-1 receptor? Further, even if the function of this protein is identified, how can this identified function of the protein relate to so many diseases? Those questions are not easy to answer and our understanding of the function of this ER protein has just begun to be unraveled.

Although the sigma-1 receptor was primarily discovered in 1982 (Su, 1982), the mechanism of action of sigma-1 receptors at the molecular level has proven difficult to find primarily because the sequence of sigma-1 receptor does not resemble any of the mammalian proteins. The cloning of the sigma-1 receptor (Hanner et al., 1996; Seth et al., 1998; Mei & Pasternak, 2001), however, played a major role in advancing the investigation. However, our understanding of the sigma-1 receptor is still limited, and the link between the current data on the mechanism of action of this receptor and the aforementioned disease states is still quite a distance away. Nevertheless, the data provide researchers some insights into potential avenues for future investigations that will hopefully lead to a more complete understanding of the relationship between sigma-1 receptors and the variety of human diseases. The same questions might be imposed on the sigma-2 receptor, as well, once the receptor is cloned in the future.

We will, thus, review the relatively well-defined major advances regarding the mechanism of action of sigma-1 receptors that have occurred within the past 10 years. The link and pathway between the basic action of sigma-1 receptors and human diseases remain to be clarified in the future. We will avoid over-speculating on this subject and will simply describe the recent findings.

Importantly, the most prominent and the most explored molecular action of sigma-1 receptors centers on the receptor's interactions with ion channels. A question naturally arises: how can an ER-resident protein such as the sigma-1 receptor interact with ion channels at the plasma membrane? A plausible explanation has been offered in a recent article, which speculates that overexpression of sigma-1 receptor agonists or administration of sigma-1 agonists might cause the translocation of sigma-1 receptors from the ER to the sub-plasma membrane area where sigma-1 receptors might interact with ion channels (Su et al., 2009). Recent progress relating sigma-1 receptors to the regulation of ion channels are reviewed below.

### 2.1. Ion channel modulation and regulation

#### 2.1.1. $Ca^{2+}$ channels

Historically, the examination of the molecular action of sigma receptors began with the studies on  $Ca^{2+}$  dynamics, which has since become the main area of sigma receptor research in terms of its molecular action.

The effects of sigma ligands on  $Ca^{2+}$  dynamics related to the intracellular  $Ca^{2+}$  stores were examined. Reduced haloperidol treatment at micromolar concentrations was found to increase intracellular calcium ( $[Ca^{2+}]_i$ ) in colon and mammary adenocarcinoma cells (Brent et al., 1996). The increase was due to the enhanced release of  $Ca^{2+}$  from intracellular stores (Brent et al., 1996). In rat cardiac myocytes, the sigma-1 receptor antagonist, BD1047, caused an increase of  $[Ca^{2+}]_i$ , and

the increase was blocked by the ER  $\text{Ca}^{2+}$ -depleting agent, thapsigargin (Novakova et al., 1998). BD-1047 was found to activate phospholipase C and elevate intracellular IP<sub>3</sub> (Novakova et al., 1998). More recent studies using molecular biological tools have clearly demonstrated that sigma-1 receptors and associated ligands modulate IP<sub>3</sub> receptors at the ER membrane. For example, the IP<sub>3</sub> receptor-inhibiting protein, ankyrin, was found to be “removed” from IP<sub>3</sub> receptors when sigma-1 receptor agonists were applied to NG-108 cells, thus enhancing  $\text{Ca}^{2+}$  efflux from the ER into the cytosol (Hayashi and Su, 2001). The same results were observed by Wu and Bowen (2008) who found that the C-terminus portion of sigma-1 receptors caused the dissociation of ankyrin from IP<sub>3</sub> receptors in MCF-7 tumor cells. In a study using CHO cells, Hayashi and Su (2007) found that sigma-1 receptors are molecular chaperones that reside specifically at the interface between the ER and mitochondria and act there as chaperones to stabilize the conformation of type-3 IP<sub>3</sub> receptors at the same interface to ensure proper  $\text{Ca}^{2+}$  signaling from the ER into mitochondria. However, sigma-1 receptors do not chaperone the type-1 IP<sub>3</sub> receptors at the general ER reticular network, and so do not affect the dynamic concentration of  $\text{Ca}^{2+}$  in the cytosol (Hayashi and Su, 2007).

Regarding the role of sigma receptors in the regulation of  $\text{Ca}^{2+}$  dynamics that are related to  $\text{Ca}^{2+}$  channels on the plasma membrane but not to intracellular  $\text{Ca}^{2+}$  stores, Zhang and Cuevas (2002) observed that sigma receptor ligands like (+)pentazocine and DTG rapidly depressed  $\text{Ca}^{2+}$  channel current, and those effects seemed to be mediated via sigma-2 receptors as the potencies of ligands in the  $\text{Ca}^{2+}$  current-depression paralleled potencies in receptor binding at sigma-2 receptors. Sigma receptor ligands seemed to block all type of  $\text{Ca}^{2+}$  channels, including the N-, L-, P/Q- and R-types, as reported in the above-mentioned study. A seminal discovery in 1990 reported that sigma-1 receptor agonists potentiate NMDA-induced neuronal firing in the CA3 region of hippocampus and that the potentiation is blocked by the sigma-1 receptor antagonist, haloperidol (Monnet et al., 1990). Monnet et al. (2003) also showed that sigma-1 receptor agonists potentiate the NMDA-induced  $\text{Ca}^{2+}$  influx from the extracellular space, and that the potentiation of the  $[\text{Ca}^{2+}]_i$  is blocked by the sigma-1 receptor antagonist, NE-100. As mentioned previously, Katnik et al. (2006) found that the ischemia-induced  $[\text{Ca}^{2+}]_i$  rise in cortical neurons was blocked by sigma-1 receptor agonists, and that the effect of the agonists was, in turn, blocked by the sigma-1 receptor antagonist, BD1047. The same group has since found that  $[\text{Ca}^{2+}]_i$  increase mediated by the acid-sensing ion channels, which are activated by  $\text{H}^+$  during ischemia and, thus, cause an increase of  $[\text{Ca}^{2+}]_i$  following ischemia, was inhibited by sigma-1 receptor agonists but not by sigma-2 agonists (Herrera et al., 2008).

### 2.1.2. Potassium channels

Using cultured frog pituitary melanotrope cells, Soriani et al. (1999a) found that the sigma-1 receptor ligands, igmesine and (+)pentazocine, dose-dependently decreased the transient outward potassium current (IA), and that the decrease was blocked by the sigma-1 receptor antagonist, NE100. Similarly, the sustained, but not the transient outward potassium current was also decreased by sigma-1 receptor agonists (Soriani et al., 1999b). The inhibition of voltage-activated potassium channels by sigma-1 receptor ligands was observed in the tumor cell line, DMS-114 (Wilke et al., 1999). However the inhibition, in contrast to that seen with the pituitary melanotropy, was insensitive to GTP (Wilke et al., 1999). Further, by using rat pituitary peptidergic terminals, Lupardus et al. (2000) found that sigma-1 receptor ligands inhibited the potassium channels in a GTP- and ATP-independent manner, and that the interaction between sigma-1 receptors and potassium channels is membrane delimited and occurs perhaps within close proximity. In an elegant study from the same research group, Aydar found that sigma-1 receptors immunoprecipitated with Kv1.4 potassium channels and that the

sigma-1 receptor acts as a ligand-regulated auxiliary potassium channel subunit with distinct functional interactions either in the presence or absence of sigma-1 receptor ligands (Aydar et al., 2002). The inhibition of potassium channels by sigma-1 receptor ligands was also found to be associated with a decrease of cyclin A expression, suggesting that sigma-1 receptor ligands might inhibit cell proliferation through cell cycle arrest (Renaudo et al., 2004). Finally, it was demonstrated that rat parasympathetic intracardiac neurons were enriched in sigma-1 receptors and that sigma-1 receptor ligands reversibly blocked delayed outwardly rectifying potassium channels, large conductance  $\text{Ca}^{2+}$ -sensitive  $\text{K}^+$  channels, and the M-current with maximal inhibition close to 80% (Zhang & Cuevas, 2005). The inhibition again did not require a cytosolic second messenger or G protein, suggesting again that sigma-1 receptors are directly coupled to potassium channels in intracardiac neurons (Zhang & Cuevas, 2005).

### 2.1.3. Sodium channels and chloride channels

Using rat medial prefrontal cortex slices, Cheng et al. (2008) found that the sigma-1 receptor agonist, DHEA sulfate, inhibited persistent sodium currents, and the inhibitory effect was ameliorated by Gi protein inhibitors and protein kinase C inhibitors. Further, other sigma-1 receptor agonists mimicked the effect of DHEA sulfate, and the effect was blocked by the sigma-1 receptor antagonist. These results suggest a sodium current-controlling mechanism via the sigma-1 receptor-Gi protein-protein kinase C signaling pathway in cortical neurons (Cheng et al., 2008).

In an interesting study examining the role of sigma-1 receptors with regards to the cell cycle in small cell lung cancer and T-cell leukemia cells, Soriani's group demonstrated that sigma-1 receptor ligands protected cancer cells from apoptosis by inhibiting volume-regulated chloride channels. Importantly, the volume measurement in hypotonic conditions revealed that the regulatory volume decrease was delayed in HEK-cells transfected with sigma-1 receptors and that the decrease was virtually abolished in the presence of the sigma-1 receptor agonist, igmesine (Renaudo et al., 2007). These data suggest that sigma-1 receptors inhibit the volume-regulated chloride channels and that sigma-1 receptor ligands further activate the channel-inhibiting activity of sigma-1 receptors.

### 2.1.4. N-methyl-D-aspartate receptor channels and long-term potentiation

As sigma-1 receptor ligands have been demonstrated in many reports to improve learning and memory in animal models of amnesia, the potential interaction of sigma-1 receptors and NMDA receptors have been an important subject in the field of sigma-1 receptor research. In fact, the first discovery that sigma-1 receptors regulate a channel came from a seminal study by Monnet et al. (1990, 2003) in which they demonstrated sigma-1 receptor ligands potentiated the NMDA-induced neuronal firing in CA3 hippocampal neurons and that the potentiation was blocked by the sigma-1 receptor antagonist. The follow-up studies of this very important discovery have been limited, especially regarding the basic molecular actions underlying the effect, though some progress has been made, as described below.

Because NMDA receptors are important for long-term potentiation, sigma-1 receptor ligands were speculated to affect learning and memory via a potential effect on the long-term potentiation (LTP) related to NMDA receptors. In fact, chronic administration of the sigma-1 receptor agonist, DHEA sulfate, in rats facilitated the induction of LTP in Schaffer collateral-CA1 synapses, and the facilitation was blocked by the sigma-1 receptor antagonist (Chen et al., 2006). Further, the DHEA sulfate ameliorated the ischemia-induced impairment of LTP correlated with the reduction of the phosphorylation of NMDA receptor subunit, NR2B (Li et al., 2006). Using patch-clamp whole-cell recording in CA1 pyramidal cells of the rat hippocampus, Martina et al. (2007) demonstrated that (+)pentazocine potentiated

NMDA receptor responses and LTP by preventing small conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^{+}$  current (SK) channels that are known to shunt NMDA receptor responses. Thus, sigma-1 receptors and associated ligands might regulate NMDA receptors and, thus, LTP by blocking the SK channel. However, Sabeti et al. (2007) demonstrated a slow-developing LTP at hippocampal CA1 synapses induced by the sigma-1 receptor agonist, pregnenolone sulfate, and found that the slow-developing LTP was independent of the NMDA receptors, but was dependent on the L-type voltage-gated  $\text{Ca}^{2+}$  channels and the sigma-1 receptor. Apparently, the interaction between sigma-1 receptors, NMDA receptors, and LTP is an important area of research that deserves more investigation.

## 2.2. Regulating signaling pathways for cell survival or cell death

This is a relatively confusing area in the field because both sigma-1 and sigma-2 receptors are involved in cell survival and cell death. In a nutshell, the general consensus is: (a) Sigma-1 receptor agonists promote cell survival and sigma-1 receptor antagonists lead to cell death and (b) Sigma-2 agonists promote apoptosis. Here, we will focus on the known pathways that relate sigma receptors to cell survival or cell death.

The sigma-1 receptor antagonist, rimcazole, was shown to inhibit tumor survival by eliciting a caspase-dependent apoptotic pathway (Spruce et al., 2004). The effect of rimcazole was at least in part due to its ability to elevate the level of hypoxia-inducible factor alpha (Achison et al., 2007). However, rimcazole is known to interact with other receptors. More selective ligands should be tested in the future in this regard. Exactly how sigma-1 receptors are related to the activation of caspases or the elevation of hypoxia-inducible factor alpha remains unknown. Haloperidol at high concentrations caused apoptosis in PC12 cells via sigma-2 receptors, perhaps by invoking Bcl-XS expression and the subsequent release of cytochrome c from mitochondria (Wei et al., 2006). The sigma-1 receptor agonist was shown in primary cortical neurons to stabilize the anti-apoptotic protein, Bcl-2 (Yang et al., 2007). The Bcl-2 preserving effect of the sigma-1 receptor agonist was blocked by the antagonist (Yang et al., 2007). In retinal ganglion cells, the neuroprotection induced by the sigma-1 receptor agonist was related to the suppression of the pro-apoptotic protein, Bax, and the prevention of the activation of caspase-3 (Tchedre & Yorio, 2008). Whether sigma-1 receptors affect those anti-apoptotic proteins at the post-translational level or at the gene regulation level is unknown at present.

## 2.3. Lipid rafts and sigma receptors

Sigma-1 receptors were found to exist on lipid rafts at the ER membrane (Hayashi & Su, 2003b). Lipid rafts are ganglioside-, sphingomyelin-, and cholesterol-enriched semi-gel lipid microdomains proposed to serve as signaling platforms for ion channels, receptors, and kinases (Simons & Ikonen, 2000). The exact relationship between sigma-1 receptors and lipid rafts is not completely clear. However, it was found that sigma-1 receptor overexpression in PC12 cells caused the reconstitution of lipid rafts by altering the gangliosides in those cells (Takebayashi et al., 2004). This study suggests that sigma-1 receptors might be related to ganglioside biosynthesis and, thus, may affect the formation of lipid rafts. The concentration of cholesterol in the lipid rafts, however, was not altered by sigma-1 receptor overexpression, as seen in the same study. The overexpression of sigma-1 receptors in PC12 cells only changed the relative distribution of cholesterol between the raft- and nonraft-fractions (Takebayashi et al., 2004). Sigma-1 receptors were recently reported to directly bind cholesterol and remodel lipid rafts in breast cancer cell lines (Palmer et al., 2007). Future studies might help establish the exact relationship between sigma-1 receptors and the formation and/or dynamics of lipid rafts.

## 3. Perspectives

Our understanding on the action of sigma-1 receptors has just begun to take shape. Despite the advancements over the past ten years defining the action of sigma-1 receptors, many questions remain unanswered. For example, regarding the interaction of sigma-1 receptors with potassium channels or acid-sensing ion channels, how could an ER-resident protein such as the sigma-1 receptor interact with ion channels on the plasma membrane considering that no cytosolic factors or G proteins are involved? Although we know that sigma-1 receptors can translocate (Morin-Surun et al., 1999; Hayashi and Su, 2003a, 2007; Mavlyutov & Ruoho, 2007), the molecular basis whereby sigma-1 receptors, an ER protein with an ER-anchoring domain and two ER transmembrane regions, might translocate and eventually bind plasma membrane proteins certainly needs clarification. Related to this point is another important question concerning the chaperone activity of sigma-1 receptors (Hayashi & Su, 2007): Do sigma-1 receptors regulate ion channels through their chaperone activities or by some other mechanism? Further, how could one protein modulate so many different classes of ion channels?

Identifying the endogenous ligands for the sigma-1 receptor and for the sigma-2 receptor, is an important problem that must be solved as well. Although the endogenous ligands for sigma-1 receptors were proposed to be neurosteroids, including pregnenolone sulfate and progesterone (Su et al., 1988), the question remains of whether other endogenous ligands might exist. Would the recently discovered *N,N*-dimethyltryptamine (Fontanilla et al., 2009) be considered as the endogenous sigma-1 receptor ligand? This is a legitimate question because the sigma-1 receptor exists not only in the brain, but also in many peripheral organs including the liver, lung, heart, adrenal gland, spleen, and pancreas (e.g., Hayashi & Su, 2007). These organs might use different endogenous ligands for the control of sigma-1 receptors and thence the organs might have different endogenous ligands and signaling targets.

Concerning the only definitive molecular action identified so far for sigma-1 receptors: Is chaperoning other proteins the only activity that sigma-1 receptors may possess? As chaperones often possess other activities, it is necessary to investigate if sigma-1 receptors might have other activities as well. A case in point would be: How do sigma-1 receptors affect lipid raft formation? Or more basically: How do sigma-1 receptors regulate the biosynthesis of gangliosides? Are any other activities of sigma-1 receptors involved? In this regard, as lipid rafts have been implicated in the entry and replication of viruses into the host cell (Schelhaas et al., 2007), the sigma-1 receptor and associated ligands might be considered for therapeutic utilization in combating viral infections.

In conclusion, in some ways the "sigma enigma" has been solved, but what comes with the unraveling of the enigma are more questions. Yet, we are in a much better position now than before to tackle more questions that include attempting to link the molecular actions of sigma-1 receptors to human diseases.

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