# Pharmacology and Therapeutic Potential of Sigma$_1$ Receptor Ligands

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**Abstract:** Sigma ($\sigma$) receptors, initially described as a subtype of opioid receptors, are now considered unique receptors. Pharmacological studies have distinguished two types of $\sigma$ receptors, termed $\sigma_1$ and $\sigma_2$. Of these two subtypes, the $\sigma_1$ receptor has been cloned in humans and rodents, and its amino acid sequence shows no homology with other mammalian proteins. Several psychoactive drugs show high to moderate affinity for $\sigma_1$ receptors, including the antipsychotic haloperidol, the antidepressant drugs fluvoxamine and sertraline, and the psychostimulants cocaine and methamphetamine; in addition, the anticonvulsant drug phenytoin allosterically modulates $\sigma_1$ receptors. Certain neurosteroids are known to interact with $\sigma_1$ receptors, and have been proposed to be their endogenous ligands. These receptors are located in the plasma membrane and in subcellular membranes, particularly in the endoplasmic reticulum, where they play a modulatory role in intracellular $Ca^{2+}$ signaling. Sigma$_1$ receptors also play a modulatory role in the activity of some ion channels and in several neurotransmitter systems, mainly in glutamatergic neurotransmission. In accordance with their widespread modulatory role, $\sigma_1$ receptor ligands have been proposed to be useful in several therapeutic fields such as amnesic and cognitive deficits, depression and anxiety, schizophrenia, analgesia, and against some effects of drugs of abuse (such as cocaine and methamphetamine). In this review we provide an overview of the present knowledge of $\sigma_1$ receptors, focussing on $\sigma_1$ ligand neuropharmacology and the role of $\sigma_1$ receptors in behavioral animal studies, which have contributed greatly to the potential therapeutic applications of $\sigma_1$ ligands.

**Key Words:** Sigma-1 receptors, learning and memory, depression and anxiety, schizophrenia, analgesia, pain, drugs of abuse, cocaine.

## 1. HISTORICAL OVERVIEW: DISCOVERY OF SIGMA RECEPTORS AND SIGMA RECEPTOR SUBTYPES

Sigma ($\sigma$) receptors were first described as a subclass of opioid receptors [102] to account for the psychotomimetic actions of ($\pm$)-SKF-10,047 (*N*-allylnormetazocine) and other racemic benzomorphans. This early confusion was due to the complex pharmacology of this racemic compound; later studies showed that ($-$)-SKF-10,047 binds to $\mu$ and $\kappa$ opioids, whereas the (+)-isomer lacks affinity for opioid receptors but binds to PCP (phencyclidine) binding sites with low affinity, and to a different site with high affinity, which currently retains the designation of $\sigma$ [reviewed in 112 and 214 amongst others].

Two different $\sigma$ sites were distinguished based on their different drug selectivity pattern and molecular mass; these two $\sigma$ sites are now known as $\sigma_1$ and $\sigma_2$ receptors [64]. It was reported that $\sigma_1$ binding sites display stereospecificity towards dextrorotatory isomers of benzomorphans, whereas $\sigma_2$ binding sites display reverse selectivity, i.e., levorotatory isomers display higher affinity than dextrorotatory isomers of $\sigma$ ligands [e.g. 64, 165]. The molecular weight was found to differ between the two $\sigma$ receptors subtypes: the $\sigma_1$ receptor is a 29-kDa single polypeptide first cloned in 1996 [55], whereas $\sigma_2$ receptors have not yet been cloned and have an apparent molecular weight of 18-21.5 kDa according to photolabeling studies [65, 159]. In spite of intensive efforts in research on the $\sigma_2$ subtype in recent years [partially reviewed in 14; 142, 156, 114], the $\sigma_1$ subtype is much better characterized, and is the focus of this review.

Sigma$_1$ receptors have been thoroughly studied in an attempt to elucidate their possible neuropharmacological applications, mainly in learning and memory processes, depression and anxiety, schizophrenia, analgesia and some effects of certain drugs of abuse. In this review we describe some aspects of the general biology of $\sigma_1$ receptors, but focus on $\sigma_1$ ligand neuropharmacology and the role of $\sigma_1$ receptors in behavioral animal studies, which have contributed greatly to the understanding of the possible neuropharmacological properties of $\sigma_1$ receptors. Non-neuropharmacological effects of $\sigma_1$ ligands such as cardiovascular effects or their effects on cancer and immunity, and their antitussive effects, are not covered in this review. Therefore this review will not go into detail on some aspects of $\sigma_1$ receptor knowledge, and not all references will be cited.

## 2. MOLECULAR CHARACTERISTICS, DISTRIBUTION AND PHARMACOLOGICAL PROFILE OF SIGMA$_1$ RECEPTORS

### 2.1. Cloning and Structure of $\sigma_1$ Receptors

Significant progress in our knowledge of $\sigma$ receptors was made when the $\sigma_1$ receptor was cloned. The $\sigma_1$ receptor is a 29-kDa single polypeptide which was first cloned in guinea-pig liver [55], and later in mouse kidney, a JAR human choriocarcinoma cell line, and in the rat and mouse brain [reviewed in 54]. The protein is composed by 223 amino acids and shows the typical $\sigma_1$ binding profile [55, 84, 180].

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The amino acid sequence of the $\sigma_1$ receptor cloned from the human cell line is highly homologous to the $\sigma_1$ receptor cloned from the other species [181], and shows no homology with other mammalian proteins, but shares approximately 30% identity with the yeast gene that encodes the C7–C8 sterol isomerase [141], and contains an endoplasmic reticulum retention signal at the $NH_2$ terminus [55, 179]. Cloning of the $\sigma_1$ receptor has contributed greatly to research in this field, making it possible to design specific antisense oligodeoxynucleotides to study $\sigma_1$ receptor function (as will be described below) and develop $\sigma_1$-receptor knockout mice [91].

Several structures have been proposed for $\sigma_1$ receptors. Initial studies proposed a single transmembrane domain structure [43, 55]. More recently, Aydar and coworkers presented evidence that the $\sigma_1$ receptor in the plasma membrane has two transmembrane segments (when expressed in *Xenopus laevis* oocytes) with the $NH_2$ and COOH termini on the cytoplasmic side of the membrane [3]. Recent studies proposed that in addition to the hydrophobic regions that constitute the putative transmembrane domains, there are two additional hydrophobic segments (one of them partially overlapping the second transmembrane domain), which were proposed to be steroid binding domain-like sites [27], and suggesting the existence of two different domains for ligand binding in the $\sigma_1$ receptor [159], as previously proposed in earlier experiments [12]. This proposed model is illustrated in Fig. (**1**). The pharmacological characterization of these putative domains merits further study.

## 2.2. Anatomical and Subcellular Distribution of $\sigma_1$ Receptors

### 2.2.1. Anatomical Distribution of $\sigma_1$ Receptors

At the anatomical level $\sigma_1$ receptors are widely distributed in peripheral organs [e.g. 192] and different areas of the central nervous system, where they have been thoroughly studied. They are widely distributed in the brain, but concentrated in specific areas involved in memory, emotion and sensory and motor functions [reviewed in 9, 54 and 146]. In these studies high to moderate levels of $\sigma_1$ receptors were associated with the hippocampus, especially in the dentate gyrus, hypothalamus, olfactory bulb, several cortical layers, pons, the septum, the central gray, locus ceruleus, dorsal raphe, the substantia nigra pars compacta, the red nucleus and various motor cranial nerve nuclei. The cerebellum is not particularly enriched in $\sigma_1$ receptors, although some of its areas, such as the Purkinje cell layer, have been reported to show considerable densities of $\sigma_1$ receptors. In addition to the brain, $\sigma_1$ receptors are also numerous in the spinal cord, mainly in the superficial layers of the dorsal horn [2].

### 2.2.2. Subcellular Distribution of $\sigma_1$ Receptors

The subcellular distribution of $\sigma_1$ receptors was firstly studied with radioligand binding in subcellular fractions, and more recently with immunochemical methods. Binding experiments with the $\sigma_1$ radioligands $[^3H](+)$-SKF-10,047, $[^3H](+)$-3-PPP and $[^3H](+)$-pentazocine showed that $\sigma_1$ receptors are located in several types of mouse, rat and guinea pig brain membrane. These binding sites are more abundant in microsomal membranes, which is consistent with the endoplasmic reticulum retention signal of the cloned $\sigma_1$ receptor [55, 179], but they are also present in nuclear, mitochondrial and synaptic membranes [17, 34, 38, 74]. Immunohistochemical studies further confirmed the existence of $\sigma_1$ receptors in the endoplasmic reticulum not only in neurons [2], but also in many other cell types such as oligodendrocytes [160], lymphocytes [43], retinal cells [76] and certain cancer cells [62]. Detailed studies by Hayashi and Su in NG108 cells showed that $\sigma_1$ receptors are located as highly clustered globular structures enriched in cholesterol and neutral lipids in the nuclear envelope and endoplasmic reticulum [reviewed in 62]. In neurons from the rat hypothalamus and hippocampus, electron microscopy studies showed that $\sigma_1$ receptor immunostaining was mostly associated with neuronal perikarya, the membrane of mitochondria, some cisternae of the endoplasmic reticulum and dendrites, where it was localized in the limiting plasma membrane including the postsynaptic thickening [2].
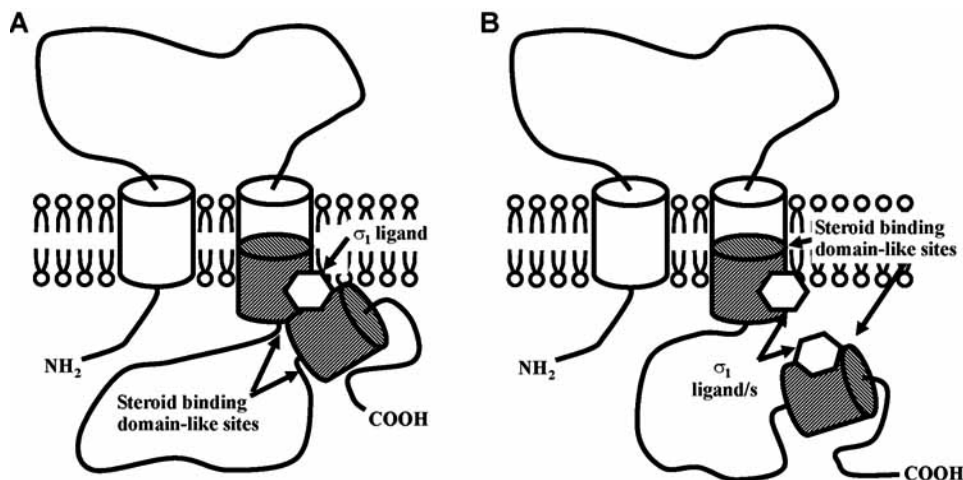


**Fig. (1).** Putative model for $\sigma_1$ receptors proposed by Pal and coworkers [159]. Open cylinders represent the two putative transmembrane domains. Closed cylinders represent the steroid binding domain-like sites and the open hexagon represents a putative $\sigma_1$ ligand. A, Possible spatial arrangement of the ligand binding site involving both steroid binding domain-like sites. B, Alternative model for ligand interaction with the $\sigma_1$ receptor.

## 2.3. Pharmacological Profile of σ₁ Receptors: Xenobiotics and Endogenous Ligands

### 2.3.1. Exogenous Ligands for σ₁ Receptors

As described in the introduction, one characteristic that distinguishes σ₁ binding sites from σ₂ receptors is that the σ₁ receptor displays stereospecificity towards dextrorotatory isomers of benzomorphans (such as SKF-10,047 or pentazocine) [64, 165]. An interesting aspect of σ₁ receptor pharmacology is that these receptors can bind, with high to moderate affinity, a wide spectrum of known compounds of very different structural classes and with different therapeutic and pharmacological applications, such as neuroleptics (e.g. haloperidol, nemopramide), antidepressants (e.g. fluvoxamine, clorgyline), antitussives (carbetapentane, dextromethorphan, dimemorfan), drugs for the treatment of neurodegenerative disorders such as Parkinson's disease (amantadine) or Alzheimer's disease (memantine, donepezil), and drugs of abuse (cocaine, methamphetamine) (Table 1). As for many other receptors, some allosteric modulators have been described for σ₁ receptors, including the anticonvulsant drugs phenytoin (DPH) and ropizine (Table 1). The modulation of σ₁ radioligand binding by DPH has been conventionally assumed to be a characteristic difference between σ₁ and σ₂ binding sites [see 121 and 165 for reviews]. However, we recently reported that DPH also discriminates between different σ₁ ligands depending on their activities on σ₁ receptors [32, 33].

Haloperidol deserves special consideration among the σ ligands, because it is the most widely used σ₁ antagonist in research on σ₁ receptors, and its affinity is high enough to bind σ₁ receptors in humans after a single oral dose [192]. In fact, haloperidol binds with similarly high affinity to dopamine D₂ receptors and σ receptors, but its metabolites display preferential activity at σ receptors compared to dopamine D₂ receptors [13]. Particularly interesting is the reduced metabolite of haloperidol (haloperidol metabolite II), which has high affinity for σ₁ and σ₂ receptors but shows much lower affinity for D₂ receptors than the original compound [13, 108]. This compound was recently shown to be an irreversible σ₁ ligand [34].

Some selective and high affinity σ₁ drugs have been developed and are considered prototypical σ₁ ligands. Examples are the σ₁ agonists (+)-pentazocine, PRE 084, JO-1784 and SA4503, and the σ₁ antagonists BD 1063 and NE-100. Table **1** summarizes the pharmacological activities on σ₁ receptors, σ subtype selectivity and other known pharmacological activities of some σ ligands used in research (and also in therapeutics). Currently the number of σ ligands is increasing rapidly with the development of new compounds [35, 98, 109, 172, among others].

### 2.3.2. Putative Endogenous σ₁ Ligands: Neurosteroids

Although the endogenous ligands for σ₁ receptors have not yet been defined unequivocally, currently the neurosteroids are considered the most probable endogenous σ₁ ligands. This term, first used by Baulieu, identifies steroids that are synthesized in the central and peripheral nervous systems, and includes pregnenolone, dehydroepiandrosterone (DHEA), their sulfate esters, progesterone, and allopregnenolone [re-

viewed in 5]. The physiological actions of neurosteroids include genomic actions and nongenomic neuromodulatory actions, the latter of which are presumably related with σ₁ receptors [see 146 for a detailed review]. The interaction between neurosteroids and σ₁ receptors was first suggested in 1988 [193] from *in vitro* experiments in guinea pig brain and spleen. Of the steroids tested, progesterone was the most potent inhibitor of σ₁-specific radioligand binding; however, whether neurosteroids are the endogenous ligands of the σ₁ receptor remains controversial because the affinity of progesterone for σ₁ receptors does not appear to be high enough for an endogenous ligand [178]. In addition, other steroids such as DHEAS (DHEA sulfate), pregnenolone sulfate, testosterone and deoxycorticosterone exhibited even lower affinities for σ₁ receptors than progesterone [61]. However, some reports support that neurosteroids are the σ₁ receptor endogenous ligands. In many experimental paradigms, progesterone behaved like other known σ₁ antagonists, and DHEA and pregnenolone sulfate act as other known σ₁ agonists [see 127 and 146 for an extensive review]. The exogenous administration of neurosteroids led to a dose-dependent inhibition of *in vivo* σ₁ radioligand binding [117, 219], and modifications in endogenous levels of neurosteroids (e.g., after adrenalectomy, castration, ovariectomy or during pregnancy) affected σ₁ responses [6, 7, 208]. The cloned σ₁ protein presents homologies with the steroid binding site of several steroidogenic enzymes, which supports the specific interaction of σ₁ receptors with neurosteroids [27, 127, 159]. We have therefore included them in Table **1** as putative σ₁ endogenous ligands.

## 3. MODULATION OF CELLULAR EFFECTS BY SIGMA₁ RECEPTORS

One of the earliest questions about the cellular effects of σ₁ receptors concerned their possible coupling to G-proteins. This issue has been studied with different experimental approaches, and the results reported to date are as profuse as they are contradictory [reviewed in 9 and 54]. Even some selective σ₁ agonists seemed to act through G-proteins (JO-1784), whereas others ((+)-pentazocine) did not under the same experimental conditions [143]. Now that the σ₁ receptor has been cloned [55], it seems clear that the cloned receptor does not have the typical structure of a G-protein-coupled receptor with seven transmembrane domains; however, the existence of a metabotropic σ₁ receptor subtype different of the cloned type cannot be ruled out yet [e.g. 104]. Although the coupling of σ₁ receptors to G-proteins remains controversial, the modulatory role of σ₁ receptors in the activity of some ion channels, different kinds of neurotransmission (mainly glutamatergic) and in second messenger systems, particularly the phospholipase C/protein kinase C/inositol 1,4,5-trisphosphate (PLC/PKC/InsP₃) system, has been extensively reported.

### 3.1. Modulation of Plasmalemmal Ion Channels

### 3.1.1. Potassium Channels

Potassium channels have been shown to constitute an important target for σ drugs. It has been shown that σ ligands inhibited $K^+$ currents in several experimental preparations [97, 103, 188, 189, 220, 224]. In some of these studies,

**Table 1.    Pharmacology of some Usual $\sigma_1$ Receptor Ligands**

| Compound | Subtype Selectivity | Affinity for $\sigma_1$ Site[*] | Function on $\sigma_1$ Site | Other Activities |
|---|---|---|---|---|
| **Benzomorphans** | | | | |
| (+)-Pentazocine | $\sigma_1$ [61] | +++ [61] | Agonist [61] | - |
| (−)-Pentazocine | $\sigma_1/\sigma_2$ [214] | ++ [214] | Agonist [31] | $\kappa_1$ agonist, $\mu_1$, $\mu_2$, ligand, low affinity $\delta$, and $\kappa_3$ opioid ligand [31] |
| (+)-SKF-10,047 | $\sigma_1$ [61] | +++ [61] | Agonist [61] | NMDA receptor ligand [61] |
| **Antipsychotics** | | | | |
| Chlorpromazine | $\sigma_1/\sigma_2$ [108] | ++ [61] | ? [61] | Dopamine $D_2$ antagonist [61] |
| Haloperidol | $\sigma_1/\sigma_2$ [61] | +++ [61] | Antagonist [61] | Dopamine $D_2$ and $D_3$ antagonist [75]; $\sigma_2$ agonist [121] |
| Nemonapride | $\sigma_1/\sigma_2$? [61] | +++ [61] | ? [61] | Dopamine $D_2$ antagonist [61] |
| **Antidepressants** | | | | |
| Clorgyline | $\sigma_1$ [74] | +++ [74] | Agonist? [9] | Irreversible monoamine oxidase A inhibitor [74] |
| Fluoxetine | $\sigma_1$ [149] | + [149] | Agonist [61] | Selective 5-HT reuptake inhibitor [149, 61] |
| Fluvoxamine | $\sigma_1$ [149] | +++ [149] | Agonist [61] | Selective 5-HT reuptake inhibitor [149, 61] |
| Imipramine | $\sigma_1$ [149] | ++ [149] | Agonist [61] | Monoamine reuptake inhibitor [61] |
| Sertraline | $\sigma_1$ [149] | ++ [149] | Agonist [9] | Selective 5-HT reuptake inhibitor [149] |
| **Antitussives** | | | | |
| Carbetapentane | $\sigma_1/\sigma_2$ [19] | +++ [19] | Agonist [121] | Muscarinic antagonist [19] |
| Dextromethorphan | $\sigma_1$ [182] | ++ [182] | Agonist [121] | NMDA receptor allosteric antagonist [93] |
| Dimemorfan | $\sigma_1/\sigma_2$ [182] | ++ [182] | Agonist [182, 217] | ? |
| **Parkinson's and/or Alzheimer's disease** | | | | |
| Amantadine | ? | + [162] | Agonist? [162] | NMDA antagonist, antiviral properties [25] |
| Donepezil | $\sigma_1/\sigma_2$? [82] | +++? [82] | Agonist [126, 136,137] | Cholinesterase inhibitor [82] |
| Memantine | ? | + [162] | Agonist? [162] | NMDA antagonist, antiviral properties [25] |
| **Drugs of abuse** | | | | |
| Cocaine | $\sigma_1/\sigma_2$ [111] | + [61, 111] | Agonist [61] | Monoamine transporters inhibitor, amongst other actions [175] |
| MDMA | $\sigma_1/\sigma_2$ [15] | + [15] | ? | Preferential SERT inhibitor, among other actions [51] |
| Metamphetamine | $\sigma_1/\sigma_2$ [151] | + [151] | ? | Preferential DAT inhibitor, amongst other actions [45] |
| **Putative endogenous ligands (neurosteroids)** | | | | |
| DHEAS | $\sigma_1$ [61] | + [61] | Agonist [61] | $GABA_A$ negative modulator [121] |
| Pregnenolone sulfate | $\sigma_1$ [61] | + [61] | Agonist [61] | NMDA positive/$GABA_A$ negative modulator [121] |
| Progesterone | $\sigma_1$ [61] | + [32, 33, 70] | Antagonist [61] | NMDA negative/$GABA_A$ positive modulator [121] |

| Compound | Subtype Selectivity | Affinity for $\sigma_1$ Site[*] | Function on $\sigma_1$ Site | Other Activities |
|---|---|---|---|---|
| **Anticonvulsants** | | | | |
| Phenytoin (DPH) | $\sigma_1$ [214] | Not applicable | Allosteric Modulator [32, 33, 214] | Delayed rectifier $K^+$ channel blocker [152]; T-type $Ca^{2+}$ current inhibitor [202]; $Na^+$ current inhibitor [177] |
| Ropizine | $\sigma_1$ [214] | Not applicable | Allosteric modulator [214] | ? |
| **Other $\sigma$ drugs** | | | | |
| BD 737 | $\sigma_1/\sigma_2$ [65] | +++ [54] | Agonist [54] | - |
| BD 1008 | $\sigma_1/\sigma_2$ [61] | +++ [61] | Antagonist [61] | $\sigma_2$ agonist? [120] |
| BD 1047 | $\sigma_1$ [107] | +++ [107] | Antagonist [107] | $\beta$ adrenoceptor ligand [107] |
| BD 1063 | $\sigma_1$ [107] | +++ [107] | Antagonist [107] | - |
| BMY 14802 | $\sigma_1/\sigma_2$ [108] | ++ [108] | Antagonist [54] | 5-$HT_{1A}$ agonist [106] |
| DTG | $\sigma_1/\sigma_2$ [61] | +++ [61] | ? [61] | $\sigma_2$ agonist [121] |
| Dup 734 | $\sigma_1$ [61] | +++ [61] | Antagonist [54] | 5-$HT_2$ antagonist [200] |
| Eliprodil (SL-82.0715) | $\sigma_1/\sigma_2$ [56] | ++ [56] | ? [61] | NMDA antagonist, $\alpha_1$ adrenoceptor ligand [56] |
| E-5842 | $\sigma_1$ [53] | +++ [53] | Antagonist [54] | Low to moderate affinity for dopamine, 5-HT and glutamate receptors [53] |
| Haloperidol Metabolite I | $\sigma_1$ [108] | ++ [34, 108] | Antagonist [22] | - |
| Haloperidol Metabolite II | $\sigma_1/\sigma_2$ [108] | +++ [34, 108] | Irreversible antagonist [34] | Dopamine $D_2$ and $D_3$ ligand [75] |
| 4-IBP | $\sigma_1/\sigma_2$ [77] | +++ [77] | Agonist [9] | Dopamine $D_2$ ligand [77] |
| JO-1784 (Igmesine) | $\sigma_1$ [61] | +++ [61] | Agonist [61] | - |
| Metaphit | $\sigma_1/\sigma_2$ [11] | ++ [34] | Irreversible antagonist [11] | Acylator of PCP and $\sigma_2$ binding sites [11] |
| (+)-MR 200 | $\sigma_1/\sigma_2$ [173] | +++ [173] | Antagonist [100] | - |
| MS-377 | $\sigma_1$ [61] | +++ [61] | Antagonist [61] | - |
| NE-100 | $\sigma_1$ [61] | +++ [61] | Antagonist [61] | - |
| OPC-14523 | $\sigma_1/\sigma_2$ [61] | +++ [61] | Agonist [54] | Agonist of pre- and post-synaptic 5-$HT_{1A}$ receptors [10]; SERT inhibitor [203] |
| Panamesine (EMD 57445) | $\sigma_1/\sigma_2$? [61] | +++? [61] | Antagonist [54] | One of its metabolites is a dopaminergic antagonist [61] |
| (+)-3-PPP | $\sigma_1/\sigma_2$ [64] | ++ [32, 33] | Agonist [61] | $\sigma_2$ agonist [121]; NMDA receptor ligand [68]; dopaminergic agonist [61] |
| PRE 084 | $\sigma_1$ [61] | +++ [61] | Agonist [61] | - |
| Rimcazole (BW-234U) | $\sigma_1/\sigma_2$ [110] | + [61] | Antagonist [61] | DAT inhibitor [110] |
| SA4503 | $\sigma_1$ [61] | +++ [61] | Agonist [61] | - |
| SR 31742A | ? | +++ [61] | ? | High affinity for C8-C7 sterol isomerase [61] |

[*] $K_i$ or $K_D$ values: +++ < 50 nM; ++ < 500 nM; + < 10 μM.

?: not studied or unclear at the moment.

-: no other pharmacological target has been described.

known $\sigma_1$ agonists and antagonists produced the same effects [220, 224]. These results might reflect the participation of $\sigma_2$ activity, since it was recently reported that $\sigma_2$ ligands can also modulate $K^+$ currents [142]. However, other recent studies showed that the selective $\sigma_1$ agonists (+)-pentazocine and JO-1784 reduced several $K^+$ currents in frog melanotropic cells [188, 189], and prevented the activation of small-conductance calcium-activated $K^+$ channels (SK channels) in rat hippocampal slices [103]. These effects were reversed by known $\sigma_1$ antagonists (NE-100 or haloperidol) [103, 188]. Regarding the molecular mechanism of the effects of $\sigma_1$ receptors in $K^+$ currents, it was proposed that $\sigma_1$ receptors and $K^+$ channels must be in close proximity for any functional interaction to occur [97, 128], and in fact the heterologous expression of $\sigma_1$ receptors with voltage-gated $K^+$ channels Kv 1.4 and 1.5, in *Xenopus* oocytes, resulted in modulation of the channel function in the absence of any $\sigma$ ligand, and greater modulation in the presence of SKF-10,047 [3]. Moreover, Kv 1.4 channel not only colocalized [128] but also co-immunoprecipitated with $\sigma_1$ receptor proteins, indicating that $\sigma_1$ receptors are directly associated with these $K^+$ channels [3]. In addition, $\sigma_1$ photolabeling with radioiodinated probes identified high-molecular-mass protein complexes, suggesting that $\sigma_1$ receptors may exist as oligomers or interact with protein partners either constitutively or through ligand binding [159]. The formation of these complexes might help explain the wide variety of actions produced by $\sigma_1$ ligands in the central nervous system.

### 3.1.2. Calcium Channels

Sigma$_1$ ligands have also been reported to modulate plasmalemmal voltage-dependent calcium channels. Interaction between $\sigma$ receptors and $Ca^{2+}$ channels was suggested from studies in which the increase in intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) mediated by depolarization was diminished by $\sigma$ ligands in neuronal cultures or forebrain synaptosomes [reviewed in 9, 54, 145]. However, in some of these experiments $\sigma_1$ agonists and $\sigma_1$ antagonists produced the same effects, which might be also due to the participation of $\sigma_2$ receptors [reviewed in 145]. In addition, the selective $\sigma_1$ agonists (+)-pentazocine and PRE 084 induced opposite effects on the increase in $[Ca^{2+}]_i$ induced by depolarization with KCl in NG108 cells, but both effects were reverted by $\sigma_1$ receptor antisense oligodeoxynucleotide [59], suggesting that they were both mediated by the cloned $\sigma_1$ receptor. It therefore seems clear that more studies are necessary to clarify the role of these receptors in plasmalemmal voltage-dependent calcium channels.

### 3.2. Neurotransmitter Systems and $\sigma_1$ Receptors: Modulation of N-methyl-D-aspartate (NMDA) Neurotransmission

Many studies have shown that $\sigma_1$ receptors are able to modulate several neurotransmitter systems. It has been reported that $\sigma_1$ receptors can potentiate glutamatergic neurotransmission [partially reviewed in 9 and 146], enhance cholinergic neurotransmission [partially reviewed in 118; 71], enhance serotonergic neurotransmission [reviewed in 9], negatively modulate the GABAergic system [47, 148], diminish noradrenaline release [20], and modulate dopaminergic neurotransmission [reviewed in 124]. The direction of

modulation of the dopaminergic system has been especially controversial because the contradictory results reported thus far make it difficult to reach solid conclusions. The conflicting results probably reflect the use of drugs with different degrees of selectivity for $\sigma_1$ receptors, and different routes of administration [reviewed extensively in 124].

Among the modulatory effects on different neurotransmitter systems by $\sigma_1$ receptors, the modulation of glutamatergic neurotransmission has been described in greater detail than others. It has been reported that $\sigma_1$ receptors can enhance spontaneous glutamate release in the hippocampus [42, 138], potentiate glutamate release induced by brain-derived neurotrophic factor [222], potentiate the increase in $[Ca^{2+}]_i$ induced by glutamate in pyramidal neurons [144], and facilitate long-term potentiation in the rat hippocampus [26, 94, 103]. Of the three subtypes of glutamate-gated ion channels (NMDA, kainate and AMPA-kainate receptors), the connection between $\sigma_1$ and NMDA receptors has been widely explored, mainly in studies of the NMDA-induced firing activity in the dorsal hippocampus. In this model $\sigma_1$ agonists such as the selective agonists JO-1784 and (+)-pentazocine, the putative agonist DHEA, and the antidepressants clorgyline and sertraline (but not paroxetine or tranylcypromine, which showed much lower affinities for $\sigma_1$ receptors) were able to modulate NMDA-induced firing. The effect of these ligands was reversed by known $\sigma_1$ antagonists such as haloperidol, NE-100 or BMY-14802, and also by the putative endogenous ligand progesterone [reviewed in 9 and 146]. Interestingly, in these studies $\sigma_1$ agonists showed a bell-shaped dose-response curve characterized by low-dose stimulation and high-dose inhibition. This type of dose-response curve indicates hormesis [18], and is well documented for $\sigma_1$ receptor activation not only in the modulation of NMDA-induced firing, but also in many other experimental approaches, as will be described below.

Particularly interesting are the studies that related steroidal tonus under physiological conditions with the $\sigma$-mediated potentiation of glutamatergic neurotransmission in the hippocampus. This effect was strongly affected by increased levels of progesterone in pregnancy [7], and by decreased levels of this neurosteroid after ovariectomy [6]. A molecular mechanism was recently proposed by which $\sigma_1$ receptor activation increases the NMDA receptor response. $Ca^{2+}$ entering the cells through the NMDA receptors activates a $Ca^{2+}$-activated $K^+$ current, underlain by SK channels, which in turn shunts the NMDA receptor responses. Selective $\sigma_1$ agonists prevented SK channel opening, and consequently increased the NMDA receptor response, emphasizing the importance of the $\sigma_1$ receptor as a postsynaptic regulator of synaptic transmission [103]. Importantly, the modulation of several neurotransmitter systems mentioned above may be a consequence, at least partially, of the modulation of NMDA receptors. It has been reported in this connection that $\sigma_1$ ligands can modulate dopaminergic [reviewed in 124], cholinergic [reviewed in 146], serotonergic [197] or noradrenergic systems [reviewed in 9] through NMDA receptors.

In summary, $\sigma_1$ receptors modulate several neurotransmitter systems, and it seems that the modulation of NMDA responses by $\sigma_1$ receptors plays a pivotal role in the modulation of neurotransmission by $\sigma_1$ ligands.

## 3.3. Sigma₁ Receptors as Modulators of Intracellular Messenger Systems

The modulation of metabotropic responses by $\sigma_1$ receptors, particularly the increase in $[Ca^{2+}]_i$ after stimulation of InsP₃ receptors at the endoplasmic reticulum, has been described in detail. The mechanism of modulation of the PLC/PKC/InsP₃ system by $\sigma_1$ receptors appears to be a complex one involving the translocation of $\sigma_1$ receptors to the plasma membrane and the nucleus; this was proposed as a mechanism by which an intracellular receptor modulates metabotropic responses [147, 59]. Sigma₁ receptors are localized in highly clustered globular structures associated with the endoplasmic reticulum, which contain moderate amounts of free cholesterol and neutral lipids, forming lipid droplets [62], in which $\sigma_1$ receptor, ankyrin (specifically the ANK220 isomer) and the InsP₃ receptors form a complex [60]. Sigma₁ receptor activation by agonists induces the dissociation of the $\sigma_1$ receptor-ANK220 complex from the InsP₃ receptors [60], potentiating the calcium efflux induced by receptors that activates the PLC system (such as receptors for bradykinin and brain-derived neurotrophic factor) [59, 60, 70, 162, 222]. The enhancement of calcium efflux, which followed a bell-shaped curve [59], has been reported not only with known selective $\sigma_1$ agonists such as PRE 084 or (+)-pentazocine [59, 60, 70], but also with other compounds such as the neurosteroids pregnenolone, pregnenolone sulfate and DHEA [59, 70], amantadine and memantine [162]. In the presence of a $\sigma_1$ antagonist, $\sigma_1$ receptors are dissociated

from ankyrin and InsP₃ receptors, which remain on the endoplasmic reticulum [60] where they impede the potentiation by $\sigma_1$ agonists of bradykinin-induced $Ca^{2+}$ efflux [59, 70, 162]. This latter effect was also prevented by the putative $\sigma_1$ antagonist progesterone [59, 70], and by specific $\sigma_1$ receptor antisense oligodeoxynucleotides [59]. Under basal conditions $\sigma_1$ ligands did not affect $[Ca^{2+}]_i$ [59, 69], and the cells needed to be stimulated to make appropriate levels of InsP₃ available for the modulation of $[Ca^{2+}]_i$ by $\sigma_1$ receptor agonists. Additionally, the silencing of InsP₃ receptors resulted in a decrease in $\sigma_1$ receptor mARN levels [154], underscoring the relationship between this second messenger system and $\sigma_1$ receptors. This proposed model of modulation by $\sigma_1$ receptors of InsP₃-mediated calcium efflux is illustrated in Fig. (**2**).

An additional mechanism by which $\sigma_1$ receptors can modulate other receptors located in the plasma membrane was recently proposed. It was reported that $\sigma_1$ receptors can affect the levels of plasma membrane lipid rafts by changing the lipid components therein [199]. This membrane reconstitution could in turn affect the function of the proteins it contains, such as neurotransmitter receptors or tropic factor receptors. In fact, $\sigma_1$ receptors play an important role in neurite sprouting [see 62 for a more complete review].

In summary, $\sigma_1$ receptors translocate from lipid droplets on the endoplasmic reticulum when stimulated by agonists, modulating intracellular $Ca^{2+}$ mobilizations at the endoplas-
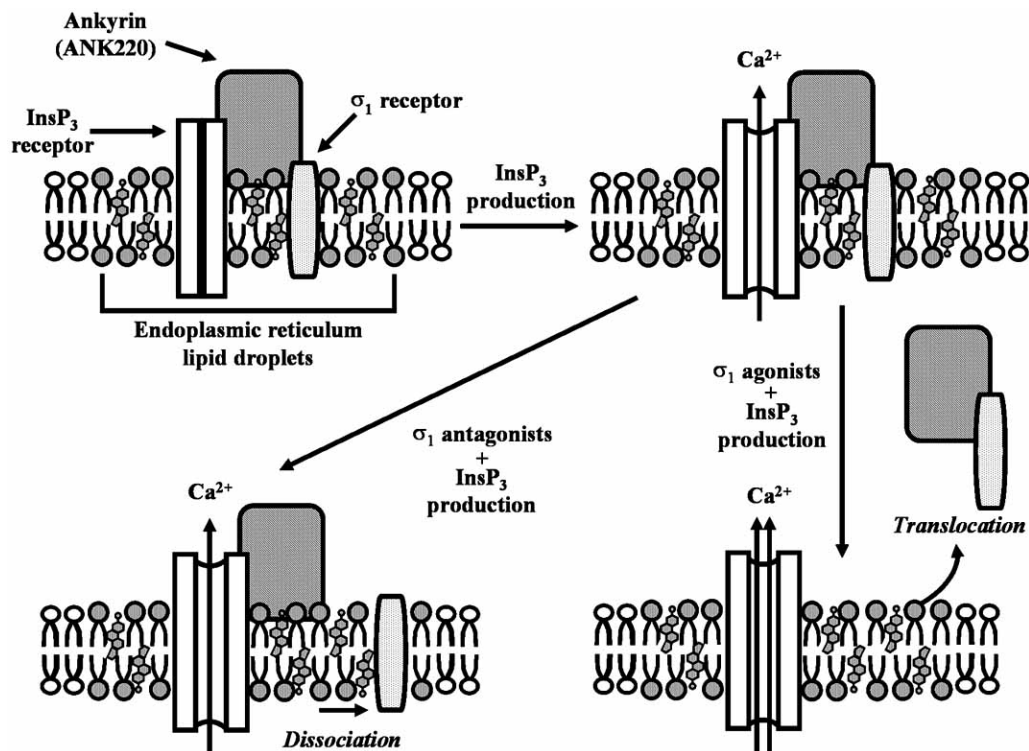


**Fig. (2).** Model of modulation by $\sigma_1$ receptors of InsP₃-mediated calcium efflux, proposed by Hayashi and Su [60, 63]. InsP₃ receptors, ANK220 and $\sigma_1$ receptor form a complex in lipid droplets on the endoplasmic reticulum, which contain moderate amounts of free cholesterol and neutral lipids. In the presence of a $\sigma_1$ agonist, the $\sigma_1$ receptor-ANK220 complex is dissociated from InsP₃ receptors and translocated. As a result InsP₃ binding to its receptor increases and $Ca^{2+}$ efflux is enhanced. In the presence of a $\sigma_1$ antagonist, ANK220 remains coupled to InsP₃ receptor, but $\sigma_1$ receptor is dissociated from the complex, impeding the potentiation of calcium efflux by $\sigma_1$ agonists.

mic reticulum after activation of the PLC/PKC/InsP$_3$ system, and enhancing the cellular effects of different receptors.

## 4. THERAPEUTIC POTENTIAL OF SIGMA$_1$ RECEPTORS

Given the widespread distribution of $\sigma_1$ receptors in the central nervous system and their modulatory role at cellular, biochemical and neurotransmission levels (see above), $\sigma_1$ ligands appear to be useful in different therapeutic fields such as depression and anxiety, amnesic and cognitive deficits, psychosis, analgesia and treatment for drugs of abuse. These potential therapeutic applications are reviewed briefly below.

### 4.1. Role of $\sigma_1$ Receptors in Learning and Memory

The central cholinergic and glutamatergic neurotransmission systems play a crucial role in learning and memory functions. Cholinergic function is disturbed in some memory pathologies such as Alzheimer's disease and pathological ageing, in which deficits in cortical cholinergic activity have been observed [4]. In addition, NMDA receptors are involved in the induction of different forms of synaptic plasticity (such as long-term potentiation) which are thought to be the synaptic substrate for learning and memory processes [166]. As described in the section 'Neurotransmitter systems and $\sigma_1$ receptors: modulation of *N*-methyl-*D*-aspartate (NMDA) neurotransmission', $\sigma_1$ agonists facilitate long-term potentiation in the rat hippocampus. However, the administration of large doses of $\sigma_1$ agonists or antagonists (+)-SKF-10,047, (+)-pentazocine, PRE 084, JO-1784, SA4503, DTG, BMY 14802, haloperidol, BD 1047 or NE-100, or even the downregulation of $\sigma_1$ receptor expression by antisense oligodeoxynucleotides, failed to affect learning in control animals. This finding suggests that $\sigma_1$ receptors are not involved in normal memory functions [see 118, 120, 121, 127, and 146 for reviews]. Bearing in mind the typical modulatory role of $\sigma_1$ receptors, it is not surprising that they have been found to modulate memory and learning processes when a state of pharmacological or pathological imbalance is induced.

### 4.1.1. Role of $\sigma_1$ Receptors in Memory and Learning Impairment Induced by Drugs, Chemicals or Brain Lesions Affecting Cholinergic or Glutamatergic Neurotransmission

The learning impairment induced by the cholinergic muscarinic antagonist scopolamine, the nicotinic antagonist mecamylamine, or by cortical cholinergic dysfunction induced by ibotenic acid injection in the basal forebrain were attenuated or reversed by several $\sigma_1$ agonists, including the selective $\sigma_1$ agonists (+)-pentazocine, JO-1874 and SA4503 [reviewed in 118, 121 and 146]. In addition, the memory impairments induced by the serotonin (5-HT) depleter *p*-chloroamphetamine (PCA), which also involves cholinergic dysfunction [115], were attenuated in a bell-shaped manner by the administration of (±)-pentazocine, (+)-3-PPP, DTG, and (+)-SKF-10,047 [115, 116]. The effects of $\sigma_1$ agonists in scopolamine-induced amnesia were reversed by known $\sigma_1$ antagonists including haloperidol and NE-100, and by the downregulation of $\sigma_1$ receptor expression by specific antisense oligodeoxynucleotides (reviewed in 118, 121 and 146). Interestingly, the putative $\sigma_1$ agonists pregnenolone

sulfate and DHEAS were also effective in scopolamine-induced amnesia model, and their effects were reversed by NE-100 and progesterone [120, 121 and 146].

As noted above, NMDA receptors also play an important role in learning and memory processes. The $\sigma$ ligands (+)-SKF-10,047, (+)-pentazocine, JO-1784, DTG, PRE 084 and SA4503, and also the putative endogenous $\sigma_1$ agonists DHEAS and pregnenolone sulfate attenuated the learning deficits induced by dizocilpine (MK-801), a noncompetitive NMDA receptor antagonist, in rats and mice presented with different mnesic tasks. The anti-amnesic effect of $\sigma_1$ agonists was reverted by several known $\sigma_1$ antagonists such as haloperidol, BMY 14802, NE-100 and BD 1047, by the putative endogenous $\sigma_1$ antagonists progesterone [partially reviewed in 120, 121 and 146; 127], and by the administration of antisense oligodeoxynucleotides against $\sigma_1$ receptors [122, 123, 126]. Cholinesterase inhibitors such as rivastigmine, tacrine and donepezil also attenuated dizocilpine-induced learning impairments [126]; however, only the effect of donepezil (which is also a potent $\sigma_1$ ligand, see Table **1**) was blocked by BD 1047 or antisense treatment [126].

Repeated exposure to carbon monoxide (CO) gas induced long-lasting but delayed amnesia which was measurable about one week after exposure. Like models of ischemia, this model involves the neurotoxicity of excitatory amino acids, and the hippocampal cholinergic system appears markedly affected by hypoxic toxicity [reviewed in 118]. Sigma$_1$ ligands have been shown to have neuroprotective properties in models of ischemia [partially reviewed in 118, 16, 81]. Consistent with this neuroprotective action is the observation that the $\sigma$ ligands (+)-SKF-10,047, PRE 084, JO-1784 and DTG reversed CO-induced amnesia, and their effects were prevented by NE-100, BMY 14802 and BD 1047 [partially reviewed in 120, 135]. Donepezil and some other cholinesterase inhibitors have also been tested in this behavioral model of amnesia, and it was found that all drugs showed anti-amnesic properties, but the pre-administration of BD 1047 blocked only the effect of donepezil [135]. Interestingly, in this model of amnesia the $\sigma_1$ antagonists BD 1008 and haloperidol also showed anti-amnesic effects that were not reversed by NE-100, so it was suggested that these drugs might produce their effects through their $\sigma_2$ agonistic activity [120]. The role of $\sigma_1$ receptors in these experimental models is summarized in Table **2**.

### 4.1.2. Role of $\sigma_1$ Receptors in Cognitive Impairments in Ageing: Alzheimer Disease

In models related with the memory deficits of ageing, $\sigma_1$ agonists were also effective in attenuating the learning deficits in aged mice, aged rats and in senescence-accelerated mice, [reviewed in 118, 146]. Moreover, in the model of Alzheimer's disease-type amnesia induced by $\beta_{25-35}$-amyloid related peptide, which involves both cholinergic and glutamatergic neurotransmission through NMDA receptors [121], the $\sigma_1$ receptor agonists (+)-pentazocine, PRE 084, SA4503, (+)-SKF-10,047, the antitussive drug dimemorfan and the putative $\sigma_1$ agonists DHEAS and pregnenolone sulfate attenuated amnesia in a bell-shaped manner. The effects of $\sigma_1$ agonists were reverted by haloperidol, BD 1047 and the putative $\sigma_1$ antagonist progesterone [119, 137, 217]. Donepezil

**Table 2.** Summary of the Effects of $\sigma_1$ Receptors in Experimental Models of Learning and Memory (see References and Text for Detailed Information)

| Involvement of $\sigma_1$ Receptors in Learning and Memory | | | | |
|---|---|---|---|---|
| Behavioral Assays | | | | |
| | | | Effect of $\sigma_1$ Agonists | Effect of $\sigma_1$ Antagonism |
| Cognitive impairment induced by | Drugs, chemicals or brain lessions | Scopolamine [121, 146] | Improvement | Reversion of the effects of $\sigma_1$ agonists |
| | | Mecamylamine [121] | Improvement | Not tested |
| | | Basal forebrain lesion [121, 146] | | |
| | | PCA [115, 116] | | |
| | | Dizocilpine [120, 121, 122, 123, 126, 127, 146] | Improvement | Reversion of the effects of $\sigma_1$ agonists |
| | | CO [16, 81, 118, 120, 135] | | |
| | Ageing-related diseases | Aged animals [146] | Improvement | Not tested |
| | | Senescence-accelerated mice [118, 146] | Improvement | Reversion of the effects of $\sigma_1$ agonists |
| | | $\beta_{25-35}$-amyloid-related peptide (Alzheimer disease-type amnesia) [119, 137, 217] | | |
| | Alterations during pregnancy | Stress [134] | Improvement | Reversion of the effects of $\sigma_1$ agonists |
| | | Cocaine administration [133] | | |
| Cognitive amelioration induced by | Low doses of cocaine [171] | | Enhancement | Inhibition |
| Effects on mechanisms involved in memory and learning impairment or potentiation | | | | |
| Impairment | Neuronal injury induced by ischemia [16, 81, 118] or $\beta_{25-35}$-amyloid-related peptide [99] | | Neuroprotective effects | Reversion of the effects of $\sigma_1$ agonists[a] |
| Potentiation | Long-term potentiation [26, 94, 103] | | Enhancement | Reversion of the effects of $\sigma_1$ agonists |

[a] Some nonselective $\sigma_1$ antagonists exert neuroprotective effects [reviewed in 118], which may be due to a non-$\sigma_1$-mediated mechanism.

and other cholinesterase inhibitors were also tested in this behavioral model, but only the effects of donepezil were partially reversed by BD 1047, suggesting that the anti-amnesic effects of this drug involve both its cholinergic and $\sigma_1$ agonistic properties [137]. These findings are consistent with the neuroprotective action of the $\sigma_1$ agonist PRE 084, which attenuated cell death in cultured cortical neurons co-incubated with $\beta_{25-35}$-amyloid related peptide, and this effect was reversed by the selective $\sigma_1$ antagonist NE-100 [99]. The effects of $\sigma_1$ ligands in ageing-related cognitive impairment are summarized in Table **2**.

### 4.1.3. Other Ameliorative Effects of $\sigma_1$ Agonists on Learning and Memory

Stress during pregnancy directly affects the neurophysiological development of the fetus with deleterious consequences observable throughout the individual's lifetime [89],

and can result in impairments in learning and memory processes [134]. The $\sigma_1$ agonist JO-1784 reversed the learning deficits induced by prenatal stress, in a BD 1063-sensitive manner [134]. In addition, it is known that repeated cocaine treatment *in utero* can induce learning and memory impairment in the offspring. It was recently found that this process can be reverted by the $\sigma_1$ agonist JO-1784 or DHEA, in a BD 1063-sensitive manner [133]. On the other hand, cocaine administered at very low doses (much lower doses than those which induce learning and memory impairments) can enhance memory storage in mice [72]. The ameliorating effects of cocaine on memory can be enhanced by the $\sigma_1$ agonist JO-1784 and also by the putative $\sigma_1$ agonist DHEA, and masked by the $\sigma_1$ antagonist BD 1047 and also by the putative $\sigma_1$ antagonist progesterone [171]. The hyperlocomotion, toxic effects, and reward properties induced by this psychostimulant are observed at much higher doses, and the effects of $\sigma_1$

ligands on these effects will be described later in section 4.5.1 on cocaine and $\sigma_1$ receptors. These effects of $\sigma_1$ agonists on cognitive impairment due to alterations during pregnancy, as well as their role in the ameliorative effects of low doses of cocaine, are summarized in Table **2**.

In summary, $\sigma_1$ agonists appear to be promising pharmacological tools against memory and learning disorders resulting from pharmacological or pathological alterations (see Table **2**). Among the memory and learning disorders, Alzheimer's disease (the most common form of late-life dementia) is characterized by a cognitive decline, and effective treatment remains elusive. Sigma$_1$ agonists could thus provide an alternative treatment against the cognitive deficits of this disease.

## 4.2. Role of $\sigma_1$ Receptors in Depression and Anxiety

Several neurotransmitter systems are important in the pathophysiology of depression and anxiety. Depression likely involves dysfunction in brain areas that are modulated by monoaminergic systems such as the frontal cortex and the hippocampus [reviewed in 39]. Given that $\sigma_1$ ligands play a modulatory role in several neurotransmitter systems, and that they can bind several known antidepressants (Table **1**), they have been studied as possible pharmacological tools against these mood disorders.

### 4.2.1. Depression and $\sigma_1$ Receptors

The effects of $\sigma_1$ ligands were tested in behavioral studies used to predict the antidepressant activity of drugs. The selective $\sigma_1$ agonists SA4503 and (+)-pentazocine decreased immobility time in the tail suspension test, and this effect was antagonized by NE-100 [207]. Many $\sigma_1$ agonists have been tested in the forced swimming test, for example SA4503, (+)-pentazocine, JO-1784, DHEAS, pregnenolone sulfate, donepezil, and some novel $\sigma$ selective compounds such as UMB23, among others. The decrease in immobility in the forced swimming test induced by the $\sigma_1$ agonists was blocked by known $\sigma_1$ antagonists [partially reviewed in 121; 126, 185, 208, 210, 218]. Interestingly, the extracts of the flowering plant *Hypericum perforatum* (St. John's wort), which are used as antidepressants, appear to exert their therapeutic actions through $\sigma_1$ receptors [reviewed in 132]. Additional experiments have related endogenous neurosteroidal levels with $\sigma_1$ receptor function. In adrenalectomized and castrated mice, the effect of JO-1784 and PRE 084 in the forced swimming test was enhanced compared to control animals, and these effects were blocked by the selective $\sigma_1$ antagonist BD 1047 [208]. In addition, the antidepressant efficacy of the selective agonist JO-1784 was enhanced in 12-month-old senescence-accelerated (SAM) mice, which showed decreased levels of progesterone [163]. Moreover, in animals acutely treated with $\beta_{25-35}$-amyloid related peptide, which does not modify their immobility time, the effects of the selective $\sigma_1$ agonists JO-1784 and PRE 084 were facilitated, presumably because of a decrease in progesterone levels in the hippocampus [209].

An important consideration is that $\sigma_1$ agonists were able to potentiate the firing of serotonergic neurons of the dorsal raphe nucleus, as early as after 2 days of treatment, whereas SSRI- and monoamine oxidase inhibitor-induced changes took several weeks to emerge. The rapid effect of $\sigma_1$ agonists has been proposed to predict a more rapid onset of antidepressant efficacy compared to existing medications [8]. Because of the typically modulatory role of $\sigma_1$ receptors, OPC-14523, a compound with high affinity for $\sigma_1$ receptors, 5-HT$_{1A}$ receptors, and serotonin transporter (SERT) (Table **1**) was developed, and was found to produce a marked antidepressant-like effect in the forced swimming test after a single oral administration. This effect was reversed by both $\sigma_1$ and 5-HT$_{1A}$ antagonists [203]. Moreover, and also in keeping with the modulatory role of $\sigma_1$ receptors, the combined administration of the selective $\sigma_1$ receptor agonist (+)-pentazocine and venlafaxine [41], or the co-administration of pramipexole and sertraline [167], at subeffective doses, showed a synergistic antidepressant-like effect, as did the co-administration of SA4503 and memantine or amantadine [186]. Importantly, the antidepressant-like effects of these drugs were reversed by known selective $\sigma_1$ antagonists, and also by progesterone [41, 167, 186].

It is known that NMDA receptor subunit 1 is decreased in the prefrontal cortex or hippocampus of depressive patients [92, 155]. In the olfactory bulbectomized rat model of depression, animals show a decrease in NMDA receptor subunit 1 in these areas, and exhibit behavioral deficits which resemble the psychomotor agitation, loss of interest, and cognitive dysfunction of depression. Repeated treatment with SA4503 ameliorated the behavioral deficits, and also reversed the decrease in the protein expression of NMDA receptor subunit 1. These effects of SA4503 were blocked by the co-administration of NE-100 and by acute treatment with the NMDA receptor antagonist dizocilpine [216]. These findings document the strong relationship between depression, NMDA receptors and $\sigma_1$ receptors.

In addition to the modulatory role of $\sigma_1$ receptors in NMDA- and 5-HT-mediated responses related with depression, a complementary mechanism of action of $\sigma_1$ ligands in this disorder has been reported to involve their effects in neuroplasticity processes. The mechanism of action of some antidepressants may involve neurotrophic actions [150], and it was reported that treatment with (+)-pentazocine or the antidepressants imipramine and fluvoxamine (which exhibit affinity for $\sigma_1$ receptors, see Table **1**) enhanced growth factor-induced neurite sprouting in PC12 cells, and also upregulated $\sigma_1$ receptors [198]. The enhancement of growth factor-induced neurite sprouting by these drugs was mimicked by the overexpression of $\sigma_1$ receptors [199].

In humans $\sigma_1$ receptors can bind fluvoxamine at therapeutic doses [73], suggesting that this receptor might mediate some of the effects of this antidepressant; it has also been reported that JO-1784, at doses of 20 mg/day, exhibited a stronger antidepressant effect than the known antidepressant fluoxetine at the same dose in clinical trials. However, at 100 mg/day JO-1784 was no different from the placebo [9], which is in keeping with the bell-shaped dose-response curves induced by $\sigma_1$ agonists in several behavioral, biochemical, and electrophysiological paradigms.

In summary, $\sigma_1$ agonists showed good antidepressant effects in several behavioral models, probably because of their enhancement of serotonergic and glutamatergic neu-

ronal functions as well as their neurotrophic actions (see Table **3**). Due to the typically modulatory role of σ₁ receptors, the design of drugs with mixed affinity for σ₁ and other receptors related with depression, and the combined treatment of σ₁ agonists with known antidepressant drugs, may offer good prospects in terms of efficacy.

### 4.2.2. Anxiety and σ₁ Receptors

Evidence of anxiolytic activity of σ₁ ligands was reported in the conditioned fear stress model, in which (+)-SKF-10,047, JO-1784, the neurosteroids pregnenolone sulfate and DHEAS, and also the antitussive dextromethorphan attenuated the motor suppression induced by previous electric footshock [79, 80, 153, 211], in a bell-shaped manner [211]. In addition, the effects of σ₁ agonists on motor suppression were reversed by the known σ₁ antagonist NE-100 and progesterone [153, 211]. In contrast, (+)-pentazocine lacked any effect in this model [79, 80]. Interestingly, the concentration of σ₁ active steroids was altered in the plasma and brain of stressed mice, and it was therefore hypothesized that endogenous levels of neurosteroids might be involved in the expression of conditioned fear stress responses *via* σ₁ receptors [153, 211]. In agreement with these results, animals treated chronically with $\beta_{1-40}$-amyloid related peptide, in which progesterone levels in the hippocampus and cortex were decreased, exhibited facilitation of the effect of the σ₁ agonists JO-1784, (+)-SKF-10,047 and DHEAS [211].

The effects of σ₁ ligands have also been assayed in other behavioral tests such as sexual dysfunction induced by stress, marble-burying behavior and colonic motor disturbances induced by fear. It was reported recently that DHEA attenuated stress-induced sexual dysfunction in rats in a NE-100 dependent manner [140]. In the marble-burying behavior test, considered a potential model of obsessive–compulsive disorder on the basis of behavioral similarity, the effect of fluvoxamine was antagonized by BD 1063 and BD 1047, but not by the σ₂ antagonist SM-21, suggesting again that the interaction of fluvoxamine with σ₁ receptors contributes to its antidepressant effects. In addition, the σ₁ agonists (+)-

SKF-10,047 and PRE 084 slightly inhibited marble-burying behavior [44]. Gue and coworkers [52] showed that JO-1784 suppressed stress-induced colonic motor disturbances induced by fear stress in rats, in a model that mimicked the gastrointestinal tract disorders frequently present in anxiety, and this effect was reversed by BMY 14802 [52]. Subsequently, JO-1784 showed good results in clinical trials in a phase-1-model of functional diarrhea [213]. The results described above (summarized in Table **4**) suggest that σ₁ receptors play an important role in the modulation of anxiety.

### 4.3. Schizophrenia and σ₁ Receptors

The dopamine hypothesis of schizophrenia, which involves enhanced mesolimbic dopamine function, remains the dominant hypothesis for the pathophysiology of this disorder, particularly regarding the appearance of positive symptoms [40]. In addition, it is important to consider the glutamatergic system. In fact, the blockade of NMDA receptors by PCP induces schizophrenia-like psychosis in humans [24, 212]. Because several antipsychotics possess high to moderate affinities for σ₁ receptors (Table **1**), researchers were inspired to test σ₁ receptor ligands in several animal models of schizophrenia.

### 4.3.1. Role of σ₁ Receptors in Behavioral Models of Schizophrenia in which Dopaminergic Function is Prominently Enhanced

In behavioral animal models in which the dopaminergic function is affected, such as apomorphine-induced climbing, amphetamine-induced locomotor activity, and behavioral sensitization by the repeated administration of psychostimulants, promising results have been reported using σ₁ antagonists (summarized in Table **5**). The nonselective σ₁ antagonist BMY 14802, panamesine, E-5842 and MS-377 inhibit apomorphine-induced climbing [53, 187, 195, 201]. In addition, DTG, SR 31742A, panamesine, rimcazole and E-5842 inhibit amphetamine-induced locomotor activity [53, 164, 176, 187]. However, rimcazole and BD 1047 had little effect on apomorphine-induced climbing, and in addition, this latter compound had little effect on acute amphetamine-induced

**Table 3.** Summary of the Involvement of σ₁ Receptors in Depression (see References and Text for Additional Information)

| Involvement of σ₁ Receptors in Depression | | Effect of σ₁ Agonists | Effect of σ₁ Antagonists |
|---|---|---|---|
| Behavioral experimental models | Tail suspension test [207] | Improvement | Reversion of the effects of σ₁ agonists |
| | Forced swimming test [121, 126, 185, 208, 210, 218] | | |
| | Olfactory bulbectomy [216] | | |
| Mechanisms associated with antidepressant activity | Firing of serotonergic neurons [8, 203] | Potentiation | Reversion of the effects of σ₁ agonists |
| | Neurotrophic actions [198] | Potentiation of growth factor-induced neurite sprouting | |
| Mechanisms associated with depression | Decrease of NMDA receptor subunit 1 [216] | Reversion | Reversion of the effects of σ₁ agonists |

**Table 4.    Summary of the Involvement of $\sigma_1$ Receptors in Anxiety (see References Cited in the Text for Detailed Information)**

| Involvement of $\sigma_1$ Receptors on Anxiety | | **Effect of $\sigma_1$ Agonists** | **Effect of $\sigma_1$ Antagonists** |
|---|---|---|---|
| Behavioral experimental models | Conditioned fear stress [79, 80, 153, 211] | Improvement | Reversion of the effects of $\sigma_1$ agonists |
| | Sexual dysfunction induced by stress [140] | | |
| | Marble-burying behavior test [44] | | |
| | Colonic motor disturbances induced by fear [52] | | |
| Clinical trials (phase-1) | Functional diarrhea [213] | Improvement | Not tested |

hyperlocomotion [187]. In models of behavioral sensitization with the repeated administration of psychostimulants—a pharmacological model of schizophrenia [21]— $\sigma_1$ antagonism inhibited sensitization to methamphetamine [1, 196, 205] and cocaine [206, 221]. It was therefore suggested that $\sigma_1$ antagonists may be suitable for maintenance therapy in persons with stable schizophrenia rather than for the treatment of acute psychotic features.

### 4.3.2. Role of $\sigma_1$ Receptors in Behavioral Models of Schizophrenia in which Glutamatergic Function is Prominently Disturbed

As said before, in addition to dopaminergic dysfunction, alterations in glutamatergic neurotransmission are also in-volved in schizophrenia. Sigma$_1$ ligands modified animal behavior in some glutamatergic models of this disease (summarized in Table **5**). PCP-induced head weaving, which is insensitive to selective D$_2$ antagonists, was attenuated by NE-100, haloperidol, BMY 14802, Dup 734 and MS-377 [63, 195]. Recent reports also showed that BD 1047, rimca-zole and panamesine attenuated PCP-induced head twitching [187]. In addition, selective $\sigma_1$ receptor agonists such as (+)-pentazocine, and also 3-(+)-PPP and (+)-SKF-10,047, en-hanced the psychotomimetic effect (hyperlocomotion) of dizocilpine in monoamine-depleted mice, and this enhance-ment was blocked by NE-100 [157], suggesting that $\sigma_1$ re-ceptor blockade may be effective for negative symptoms of schizophrenia, which are hypothesized to be mediated, at

**Table 5.    Summary of the Involvement of $\sigma_1$ Receptors in Schizophrenia (see References and Text for Detailed Information)**

| Involvement of $\sigma_1$ Receptors on Schizophrenia | | | **Effect of $\sigma_1$ Agonists** | **Effect of $\sigma_1$ Antagonists** |
|---|---|---|---|---|
| Behavioral experimental models | Dopaminergic function prominently enhanced | Apomorphine-induced climbing [53, 187, 195, 201] | Not tested | Inhibition |
| | | Amphetamine-induced locomotor activity [53, 164, 176, 187] | | |
| | | Behavioral sensitization induced by repeated administration of psychostimulants [1, 196, 205, 206, 221] | | |
| | Glutamergic function prominently disturbed | PCP-induced stereotyped behaviors [63, 187, 195] | Not tested | Inhibition |
| | | Dizocilpine-induced hyperlocomotion in monoamine depleted mice [157] | Enhancement | Reversion of the effects of $\sigma_1$ agonists |
| | | PCP-induced cognitive deficits [58] | Improvement | Reversion of the effects of $\sigma_1$ agonists |
| Clinical trials | Only with BMY 14802, eliprodil and panamesine [61] | | Not tested | Inconclusive results |

least in part, by glutamatergic neurotransmission. Among the negative symptoms of schizophrenia, cognitive deficits are core features of the illness and predict vocational and social disabilities for patients [90]. It has been extensively reported that $\sigma_1$ agonists play an important role in memory processes (as described in the section 4.1., 'Role of $\sigma_1$ receptors in learning and memory'). In fact, SA4503, DHEAS, and flu-voxamine (a SSRI with high affinity for $\sigma_1$ receptors), but not paroxetine (an SSRI without affinity for $\sigma_1$ receptors) improved the PCP-induced cognitive deficits in the novel object recognition test, and these effects were antagonized by the co-administration of NE-100 [58]. In addition, the antipsychotic (and also $\sigma_1$ antagonist) drug haloperidol was ineffective in this behavioral model [57]. These results suggest that $\sigma_1$ agonists are potentially useful for the cognitive deficits of schizophrenia.

### 4.3.3. Sigma₁ Receptors and Extrapyramidal Side Effects

The extrapyramidal effects of neuroleptics are considered one of the most problematic side effects of these drugs. It has been suggested that $\sigma$ receptors mediate the undesirable motor side effects of antipsychotic drugs [reviewed in 54 and 214], an effect classically attributed to the $\sigma_2$ subtype [e.g., 215]. Although it was found that the affinities of several neuroleptics for $\sigma$ receptors (both $\sigma_1$ and $\sigma_2$) correlated well with their risk of producing acute dystonic reactions [108], it is known that the blockade of $\sigma_1$ receptors with other more selective antagonists such as NE-100 [158], MS-377 [195], E-5842 [53] or BMY 14802 [50] (at effective doses for the test used) does not induce motor side effect. These findings suggest that the blockade of $\sigma_1$ receptors is not enough in itself to induce extrapyramidal side effects, so additional mechanisms are probably be involved.

### 4.3.4. Clinical Trials with σ₁ Ligands in Schizophrenia

Some clinical trials have been done with rimcazole, BMY 14802, eliprodil (SL-82.0715) and panamesine. The trials with rimcazole and BMY 14802 yielded inconclusive results [reviewed in 61]; however, eliprodil reduced scores for negative but not positive symptoms, whereas panamesine reduced both positive and negative symptoms. However, a metabolite of panamesine has potent antidopaminergic properties which might explain its effect against the positive symptoms, so further research is needed to determine whether these effects are wholly or partly mediated by $\sigma_1$ receptors [reviewed in 61].

In summary, due to the complex pathogenesis of schizophrenia and the differential effects of $\sigma_1$ antagonists (which improve the behavior of animals in models based on the motor effects of dopaminergic stimulants or NMDA antagonists) and $\sigma_1$ agonists (which improve the cognitive deficits induced by PCP) (summarized in Table **5**), treatment based exclusively on $\sigma_1$ ligands would probably be complex.

### 4.4. Sigma₁ Receptors and Analgesia

Sigma$_1$ receptors are distributed in the central nervous system in areas of great importance in pain control, such as the superficial layers of the spinal cord dorsal horn, the periaqueductal gray matter, the locus ceruleus and rostroventral medulla [2, 88]. As will be described below, they may be involved in the modulation of opioid analgesia, and may also play an important role in nociception in the absence of opioid drugs.

### 4.4.1. Modulation of Opioid Analgesia by σ₁ Receptors

Chien and Pasternak were the first to report the involvement of $\sigma_1$ receptors in analgesia [28]: they clearly demonstrated that $\sigma_1$ receptors play an important role in the modulation of opioid analgesia in the tail-flick test. The systemic administration of $\sigma_1$ agonists, including the selective $\sigma_1$ agonist (+)-pentazocine, antagonized the antinociception induced by morphine in the tail-flick test [28-30, 130]. Further experiments with other opioids confirmed the role of $\sigma_1$ receptors in opioid analgesia. (+)-Pentazocine also diminished $\delta$-, $\kappa_1$-, and $\kappa_3$-opioid antinociception [29, 130, 173]. In addition, $\sigma_1$ antagonists such as haloperidol and (+)-MR 200 not only reversed the effects of agonists, but also increased opioid-induced antinociception, indicating the presence of a tonically active anti-opioid $\sigma_1$ system [28-30, 100, 173].

The anatomical location of the modulation of opioid analgesia by $\sigma_1$ receptors has been determined with different routes of administration of opioids, $\sigma_1$ receptor ligands and antisense oligodeoxynucleotides. The intrathecal (i.t.) administration of (+)-pentazocine did not reverse the spinal (i.t.) analgesic effect of morphine in the tail-flick test, suggesting that the modulation of opioid analgesia by $\sigma_1$ receptors in this test does not occur at the spinal level [130]. Interestingly, the supraspinal (intracerebroventricular, i.c.v.) administration of (+)-pentazocine decreased the analgesic effect of agonists for the $\kappa$ and $\mu$ opioid receptors nalorphine and nalbuphine [130]; in addition, the analgesia induced by the supraspinal (i.c.v.) administration of the selective $\mu$-opioid agonist DAMGO was enhanced by the $\sigma_1$ antagonist (+)-MR 200 administered subcutaneously [100]. Further experiments based on the selective blockade of $\sigma_1$ receptor synthesis by the i.c.v. administration of specific antisense oligodeoxynucleotides confirmed the supraspinal location of the modulation of opioid analgesia [87, 130, 161]. Finally, a more detailed approach was tested recently by Mei and Pasternak [131], who used microinjections of morphine in conjunction with (+)-pentazocine, haloperidol, or both in three brainstem nuclei: the periaqueductal gray, rostroventral medulla and locus ceruleus. The activity of $\sigma_1$ receptors was found to differ depending on the area. Whereas both the locus ceruleus and rostroventral medulla were sensitive to (+)-pentazocine, the periaqueductal gray was not. The rostroventral medulla was particularly interesting, because it was the only region with evidence for tonic $\sigma_1$ activity (enhanced by haloperidol), and it was also able to modulate the analgesia from morphine administered to the periaqueductal grey.

In contradistinction to results in the tail-flick test, it was found that the systemic administration of (+)-SKF-10,047 or NE-100 was unable to modulate $\kappa_1$ opioid analgesia in the acetic acid-induced writhing test [66]. Although the doses used in this study might have been too low to prevent the participation of $\sigma_1$ receptors in the modulation of $\kappa_1$ opioid analgesia in the acetic acid-induced writhing, i.c.v. treatment with $\sigma_1$ antisense oligodeoxynucleotides also failed to affect this response [67], suggesting that the supraspinal inhibition

of $\sigma_1$ receptors does not affect $\kappa$ opioid analgesia in this behavioral test. This findings may indicate that the supraspinal $\sigma$ system modulates only some opioid analgesic effects, probably depending on the type of pain evaluated (i.e., depending on the behavioral model used). Further research with different models is needed to characterize the role of the supraspinal $\sigma$ system in opioid analgesia. The role of $\sigma_1$ receptors on opioid analgesia in behavioral experimental models is summarized in Table **6**.

In addition, some recent reports showed that haloperidol and chlorpromazine, two neuroleptics that bind to $\sigma$ sites (Table **1**), inhibit the antianalgesia induced by nalbuphine in men [48]. Although the authors did not attribute this inhibition to $\sigma$ receptors, this possibility cannot be fully ruled out, and would suggest that interaction between the $\sigma$ and opioid systems is important in clinical terms. However, this issue also needs to be addressed in further clinical studies.

### 4.4.2. Analgesic Effect of $\sigma_1$ Receptor Ligands

The role of $\sigma_1$ ligands in the absence of opioid drug has also been investigated. Several $\sigma_1$ ligands or antisense treatments have been proved to be inactive in the tail-flick test [22, 28-30, 100, 130, 161], as well as in the acetic acid-induced writhing test [66, 67] (although higher doses of $\sigma_1$ ligands should be tested to ensure their lack of involvement in acetic acid-induced writhing). However, other reports showed that $\sigma_1$ receptors are able to modulate nociception in other behavioral tests in the absence of an opioid drug. Ueda and coworkers [204] showed that the $\sigma_1$ agonists (+)-pentazocine and SA4503, (+)-3-PPP, and also the putative $\sigma_1$ agonists DHEAS and pregnenolone sulfate (administered intraplantarly) can induce nociception even when used alone in the nociceptive flexor response test. The effect of the $\sigma_1$ ago-

nists was reverted by the known $\sigma_1$ antagonists NE-100, BD 1047 or the putative $\sigma_1$ endogenous antagonist progesterone [204]. Other studies in our laboratory with the formalin test showed that formalin-induced nociception was attenuated not only by the systemic administration of haloperidol, haloperidol metabolite II and haloperidol metabolite I (with an order of potency which correlated with their affinity for $\sigma_1$ receptors) [22], but also in $\sigma_1$ receptor knockout mice [23]. Recent experiments with the same behavioral test found that in contradistinction to the supraspinal action of $\sigma_1$ antagonists on the modulation of opioid analgesia, the i.t. administration of the $\sigma_1$ receptor antagonists BD 1047 and BMY 14802 dose-dependently reduced formalin-induced pain behaviors in the second phase but not in the first phase of the formalin test [86]. This underscored the importance of spinal $\sigma_1$ receptors in the second phase of formalin-induced pain. These results were consistent with previous findings which showed that haloperidol, haloperidol metabolite I and haloperidol metabolite II were more effective in the second than in the first phase of formalin-induced pain [22]. In agreement with these behavioral studies, it was also reported that antagonism of spinal $\sigma_1$ receptors suppressed phosphorylation of the NR1 subunit of spinal NMDA receptors [86], which are important for maintaining spinal sensitization associated with the second phase of the formalin test [190]. From these results it was proposed that $\sigma_1$ receptors may be important in models in which spinal sensitization occurs (without ruling out other analgesic effects in other models), and in fact, the putative $\sigma_1$ agonist DHEA induced mechanical allodynia and thermal hyperalgesia when administered i.t., and the effects were reversed by BD 1047 [85]. This hypothesis deserves further investigation in other models of pain, especially in models of tonic pain in which central sensitization occurs. The results obtained in the behavioral mod-

**Table 6.    Summary of the Involvement of $\sigma_1$ Receptors in Analgesia (see Text and References for Detailed Information, as Administration Routes of Drugs)**

| | Behavioral Experimental Models | Effect of $\sigma_1$ Agonists | Effect of $\sigma_1$ Antagonism |
|---|---|---|---|
| **Involvement of $\sigma_1$ Receptors on Analgesia** | | | |
| Modulation of opioid analgesia | Tail-flick test [28-30, 87, 100, 130, 161, 173] | Inhibition | Enhancement |
| | Acetic acid-induced writhings [66, 67] | Inactive (very low doses tested)[a] | Inactive (very low doses tested)[a] |
| Pain modulation in the absence of opioid drugs | Tail-flick test [22, 28-30, 100, 130, 161] | Inactive | Inactive |
| | Acetic acid-induced writhings [66, 67] | Inactive (very low doses tested)[a] | Inactive (very low doses tested)[a] |
| | Nociceptive flexor response test [204] | Nociception | Reversion of the effects of $\sigma_1$ agonists |
| | Formalin-induced pain [22, 23, 86] | Reversion of the effects of $\sigma_1$ antagonists | Antinociception |
| | Plantar test [85] | Thermal hyperalgesia[b] | Reversion of the effects of $\sigma_1$ agonists |
| | von Frey test [85] | Mechanical allodynia[b] | Reversion of the effects of $\sigma_1$ agonists |

[a] Additional experiments using higher doses of $\sigma_1$ ligands should be performed.

[b] Selective $\sigma_1$ agonists should be tested.

els described above (summarized in Table **6**) suggest that σ₁ receptors play an important role in nociception in the absence of opioid drugs.

In summary, σ₁ receptors are not only able to modulate opioid antinociception, at least in the tail-flick test, but may also play an active role in nociception in the absence of opioid drugs in some behavioral models (see Table **6**).

### 4.5. Sigma₁ Receptors and Drugs of Abuse

As shown before (Table **1**), σ₁ receptors can bind several drugs of abuse. It is therefore not surprising that σ₁ ligands can modulate some of the effects of these drugs. Among the drugs of abuse studied to date, the involvement of σ₁ receptors in the actions of cocaine has been extensively investigated, but σ₁ receptors also appear to underlie the effects of other substances such as methamphetamine, MDMA (3,4-methylenedioxymethamphetamine) and ethanol, as will be described below.

### 4.5.1. Cocaine and σ₁ Receptors

Cocaine is generally thought to act as a dopamine re-uptake inhibitor to produce its reinforcing effects, although other mechanisms might also be important [105]. Cocaine binds preferentially to σ₁ receptors rather than to σ₂ [111], and the affinity of cocaine for σ₁ receptors is in the micromolar range (Table **1**), as is its affinity for its main pharmacological target, the dopamine transporter (DAT) [175]. Cocaine levels in the post-mortem brain of addicts were estimated to be between 0.1 and 4 μM [78], which is close to the $K_i$ value of cocaine for σ₁ receptors. In recent years several excellent and promising studies have been performed with σ₁ ligands against the effects of cocaine, as described below.

#### 4.5.1.1. Modulation by σ₁ Receptors of the Acute Effects of Cocaine

The ability of compounds to attenuate the acute locomotor effects of cocaine is often used as an initial screening tool to identify agents able to block the psychostimulant activity of this drug of abuse. Convulsions and lethality, on the other hand, represent a measure of cocaine toxicity, and can result from exposure to acute large doses. Many σ₁ antagonists have been reported to significantly prevent the acute locomotor stimulatory effects, convulsions or lethality induced by cocaine in rodents, including haloperidol, BD 1008 (and some of its analogs such as the selective σ₁ antagonists BD 1047 and BD 1063), BMY 14802, panamesine and rimcazole (and some of its analogs), among others [partially reviewed in 112 and 124; 37, 95, 113]. Furthermore, the administration of antisense oligodeoxynucleotides that knock down brain σ₁ receptors mimicked the effects of pharmacological σ₁ antagonism on the locomotor stimulatory effects or convulsions induced by cocaine [109, 111]. Particularly interesting are the studies in which post-treatment of mice with the novel σ receptor antagonists LR132 and YZ-011, after cocaine administration, also attenuated cocaine-induced lethality after an overdose. However, BD 1063 was unable to prevent death under these conditions, and the authors hypothesized that this result was due to differences in pharmacokinetics [109, 111]. The ability of σ receptor antagonists to prevent death after an overdose of cocaine in animals sug-

gests a clinical application potentially worth further study. In contradistinction to the positive effects of σ₁ antagonists, the administration of DTG, the novel σ₁ agonists BD1031 and BD1052, or the selective σ₁ agonist SA4503 exacerbated locomotor stimulatory actions and the toxic effects (measured as convulsions and lethality rate) of the acute administration of cocaine [109, 111, 129, 184]. The results obtained in these behavioral models (summarized in Table **7**) suggest that σ₁ receptors play an important role in the acute effects of cocaine. In addition to σ₁ receptors, it has been proposed that the σ₂ subtype might also be a good pharmacological target against cocaine-induced actions [partially reviewed by 113; 114, 156].

#### 4.5.1.2. Modulation by σ₁ Receptors of the Effects of Repeated Cocaine Administration

Several σ₁ antagonists have also been tested in behavioral models that used repeated doses of this drug of abuse. The σ₁ antagonists rimcazole and some of its analogs, and other putative σ antagonists did not alter or only slightly altered the discriminative stimulus of cocaine [83, 95, 221], indicating that the interaction between cocaine and σ receptor ligands might be more complex than an exclusively competitive antagonism. Other studies that involved the repeated administration of cocaine found that σ receptor antagonists significantly prevented the development of cocaine-induced locomotor sensitization [206, 221], which is considered a measurable index of nervous system plasticity resulting from repeated exposure to cocaine [112]. The effects of σ₁ antagonism on the rewarding properties of this drug of abuse have been explored with promising results. In the conditioned place preference test, the selective σ₁ receptor antagonists BD 1047 and NE-100 attenuated the acquisition [168, 169] and also the expression of cocaine-induced conditioned place preference [169]. In addition, treatment with σ₁ antisense oligodeoxynucleotide was effective against the acquisition of conditioned place preference, indicating the specificity of these effects [168]. However, in cocaine self-administration experiments, Martin-Fardon and coworkers found that BD 1047 was inactive against the acute reinforcing effects of cocaine, supposedly because both the reinforcing quality and relevant neuroadaptive changes are likely to differ in rats subjected to involuntary administration (as in conditioned place preference) vs. self-administration of cocaine [101]. After extinction, cocaine addictive behavior can be reactivated by a discriminative stimulus associated with cocaine administration, or by a priming injection of cocaine (in self-administration or conditioned place preference experiments, respectively). These processes were both blocked by BD 1047 [101, 170], and the latter one was also blocked by σ₁ antisense oligodeoxynucleotides [170]. Interestingly, the σ₁ agonists PRE 084 and JO-1784 were unable to induce conditioned place preference [169], but the administration of the latter σ₁ agonist, or even DHEA, was enough to reactivate conditioned place preference after extinction, in a BD 1047-sensitive manner [170]. The results in these behavioral models (summarized in Table **7**) suggest that σ₁ receptors play an important role in neuronal plasticity after repeated cocaine administration, and that σ₁ antagonists could be useful to prevent craving and relapse of cocaine addiction.

**Table 7.    Summary of the Involvement of $\sigma_1$ Receptors in the Behavioral Effects Induced by Cocaine (see References and Text for Detailed Information)**

| Involvement of $\sigma_1$ Receptors in Cocaine-Induced Behavioral Effects | | | Behavioral Experimental Model | Effect of $\sigma_1$ Agonists | Effect of $\sigma_1$ Antagonism |
|---|---|---|---|---|---|
| Acute effects of cocaine | Psychostimulant effects | | Locomotor activity [37, 95, 111, 109, 112, 124] | Potentiation | Inhibition |
| | Toxicity | | Convulsions [37, 109, 111, 112, 113, 124] | | |
| | | | Lethality [37, 112, 113, 124] | | |
| Repeated administration of cocaine | Self-reported effects of cocaine | | Drug discrimination test [83, 95, 221] | Not tested | Slight or no effect |
| | Nervous system plasticity | | Locomotor sensitization [206, 221] | Not tested | Inhibition |
| | Rewarding properties | During addictive behavior | Conditioned place preference [168, 169] | Not tested | Inhibition |
| | | | Self-administration [101] | Not tested | No effect |
| | | After extinction of addictive behavior | Conditioned place preference after priming injection of drugs [170] | Reactivation | Inhibition |
| | | | Discriminative stimulus associated with cocaine availability for self-administration [101] | Not tested | Inhibition |

It has been reported that $\sigma_1$ receptor density changes after repeated treatment with cocaine [96, 169, 170, 183, 223]. Particularly interesting is the $\sigma_1$ receptor upregulation in the caudate putamen (an important area in the drug reward mechanism), which was not produced in dopamine $D_1$ receptor knockout mice [223]. Consistent with this finding was that cocaine treatment in the neuroblastoma cell line B-104 (lacking in dopamine transporter or receptors), was also unable to induce $\sigma_1$ receptor upregulation [36], suggesting a close relationship between dopamine and $\sigma_1$ receptors. In fact, it has been proposed that both $D_1$ receptors and $\sigma_1$ receptors are involved in cocaine-induced life-long alterations in neurons [194].

#### 4.5.1.3. Effects of $\sigma_1$ Ligands on Cocaine-Induced Immune System Depression

Different experiments have been designed to investigate the effects of cocaine other than its acute toxicity or rewarding properties, specifically, modulation of the immune system by cocaine. It was recently reported that cocaine can enhance alveolar cell carcinoma growth in mice, and that this effect was mimicked by PRE 084 and reversed by BD 1047. Increased tumor growth induced by cocaine or PRE 084 was accompanied by an increase in IL-10 and a decrease in IFN-$\gamma$ production [46]. In addition, the selective $\sigma_1$ antagonist

BD 1047 blocked enhancement of the replication of HIV-1 in mice with severe combined immunodeficiency implanted with HIV-1-infected human peripheral blood mononuclear cells [174], and also in human microglial cell cultures [49]. These reports suggest that $\sigma_1$ receptors are involved in the cocaine-induced depression of the immune system.

In summary, $\sigma_1$ antagonists appear to be potentially useful not only against acute cocaine toxicity or addiction, but also against the noxious modulation of the immune system in cocaine consumers. In addition, $\sigma_1$ agonists, as described in section 4.1. 'Role of $\sigma_1$ receptors in learning and memory,' may be useful against some behavioral alterations induced by repeated cocaine exposure *in utero*. It therefore seems clear that cocaine produces its behavioral and biochemical effects, at least in part, through its interaction with $\sigma_1$ receptors, and that $\sigma_1$ ligands should be considered for the development of potential therapies to treat different aspects of cocaine abuse.

#### 4.5.2. Other Drugs of Abuse and $\sigma_1$ Receptors

Methamphetamine, like cocaine, also binds to $\sigma_1$ receptors in the micromolar range (Table **1**), and with a 20-fold higher affinity than for $\sigma_2$ receptors [151], so it is not unexpected that $\sigma_1$ ligands modulate some effects of this psychostimulant. Early studies found that the $\sigma_1$ antagonists NE 100, BMY 10802 and MS-377 modulated the acute motor

effects of methamphetamine only weakly, if at all [158, 196, 205]. However, more recent studies showed that the selective $\sigma_1$ antagonists BD 1063 and BD 1047, as well as $\sigma_1$ antisense oligodeoxynucleotide, inhibited methamphetamine-induced locomotor activity [151]. It was also recently reported that like cocaine or methamphetamine, the compound MDMA ('ecstasy'), which is structurally related to methamphetamine, showed preferential affinity for $\sigma_1$ receptors rather than for the $\sigma_2$ subtype, and that BD 1063 also attenuated the locomotor activity induced by this compound [15]. Furthermore, BMY 14802 and MS-377, two known $\sigma_1$ antagonists, inhibited the behavioral sensitization induced by the repeated administration of methamphetamine [1, 196, 205]. As in studies with repeated cocaine administration, it was thought that $\sigma_1$ receptors might play a role in neuronal plasticity after the repeated administration of methamphetamine. Sigma$_1$ receptor levels were recently found to be unaltered in rats passively treated with this psychostimulant; however, in rats self-administered with methamphetamine, $\sigma_1$ receptors were upregulated in the rat midbrain, an area involved in learning and reward processes, but not in the cerebellum, frontal cortex, striatum and hippocampus. These observations underscored the role of $\sigma_1$ receptors in neuronal plasticity after the consumption of psychostimulants [191].

The role of $\sigma_1$ receptors in the behavior of other drugs of abuse has also been explored, and it was found that the $\sigma_1$ antagonist BD 1047 was effective against ethanol-induced locomotor stimulation, conditioned place preference, taste aversion and some symptoms of the abstinence syndrome after chronic ethanol consumption [125, 135]. Interestingly, $\sigma_1$ receptor expression was increased in the hippocampus of mice after chronic ethanol consumption. However, both the $\sigma_1$ agonist JO-1784 and the antagonist BD 1047 shared some ameliorating properties against the abstinence syndrome after chronic ethanol consumption [135]. These observations suggest a new pharmacological target for alleviating ethanol addiction and abstinence syndrome after withdrawal, although more behavioral tests should be performed. Interestingly, an association has been suggested between polymorphisms in the $\sigma_1$ receptor gene and alcoholism [139], supporting the role of $\sigma_1$ receptors in chronic ethanol consumption.

## 5. CONCLUSIONS AND PERSPECTIVES

At the present time it seems logical to attribute the neuropharmacological properties of $\sigma_1$ ligands to the neuromodulatory role of $\sigma_1$ receptors. They act as intracellular amplifiers for signal transductions involving InsP$_3$ receptors, are clearly able to modulate neurotransmitter systems (mainly through NMDA receptors) and ion channels (such as K$^+$ channels), and may play an important role in neuroplasticity processes. Because of this typically modulatory nature of $\sigma_1$ receptors, $\sigma_1$ ligands are usually devoid of effect *per se* under control conditions in many experimental situations. In fact, and in agreement with the modulatory role of $\sigma_1$ receptors, $\sigma_1$ knockout mice do not display any overt phenotype. However, data showed that $\sigma_1$ ligands are highly active when a pharmacological or pathological imbalanced state arises. In addition, and also due to the modulatory role of $\sigma_1$ receptors, the combined administration of $\sigma_1$ receptor ligands and

medications with a known therapeutic effect has been shown to improve the effects of the latter (at least in behavioral models of depression and in opioid-mediated analgesia), resulting in the need for lower doses to reach therapeutic concentrations. This synergistic action of $\sigma_1$ ligands and low doses of other known drugs merits further study in additional behavioral models. Of particular interest is the bell-shaped dose-response curve of $\sigma_1$ agonists in *in vitro* experiments, in behavioral tests in which $\sigma_1$ agonists are active (i.e., learning and memory processes, depression and anxiety), and even in some clinical trials. These data strongly suggest that researchers should take hormesis into account in order to design informative experiments or clinical trials with $\sigma_1$ agonists.

In the light of our current knowledge, it seems clear that $\sigma_1$ agonists are promising pharmacological tools against memory and learning disorders, and also against depression and anxiety. Although some previous findings suggest that $\sigma_1$ antagonists might be potentially useful tools against some symptoms of schizophrenia, currently the most promising therapeutic targets for $\sigma_1$ antagonism are nociception and some deleterious effects of certain drugs of abuse (such as cocaine, methamphetamine and ethanol). Importantly, many drugs used routinely in therapeutics show affinity for $\sigma_1$ receptors (see Table **1**), and exert the same effects as other more selective $\sigma_1$ ligands in many behavioral tests and *in vitro* assays. Therefore, the therapeutical properties of these drugs might be due, at least in part, to their interaction with $\sigma_1$ receptors. Interestingly, several drugs have been proved to be effective against diseases (in behavioral animal models) different from those for which they are prescribed in clinical practice, through their interaction with $\sigma_1$ receptors. These findings raise the possibility of new therapeutic applications with drugs routinely used in therapeutics.

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