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REVIEW ARTICLE

THE SIGMA-1 (σ_1) RECEPTOR AND ITS ROLE IN THE TREATMENT OF MOOD DISORDERS

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ABSTRACT

Sigma (σ) receptors have long been implicated in a variety of neuronal and brain functions, although their precise biochemical and physiological role, and potential involvement in neurological and psychiatric disorders, remains elusive. However, nearly 30 years after their characterization, evidence arising from various research fields has begun to unveil the biological function and clinical implications of σ receptors. These receptors are intracellular molecules consisting of at least two subtypes – σ_1 and σ_2. The σ_1 receptor, an integral membrane protein with two transmembrane domains, mainly localizes at the endoplasmic reticulum (ER). A recent study identified the σ_1 receptor as possessing innate biological activity as a molecular chaperone, activity that can be activated/inactivated by synthetic compounds that bind to σ_1 receptors. The σ_1 receptor regulates Ca^{2+} signaling, ion channel activity, trophic factor signaling, cell survival, myelination and synaptogenesis. Certain clinically used antidepressants and steroids bind to the σ_1 receptor, and selective σ_1 agonists have demonstrated relatively rapid antidepressant-like actions in preclinical studies; such agents have been introduced into clinical trials. The recent discoveries regarding the hitherto enigmatic σ receptor have fueled expectation that this receptor class may provide novel opportunities for pharmacological interventions. In this review, we present current data supporting the notion that this novel ligand-operated molecular chaperone may provide a new intracellular target for future therapeutic agents.

INTRODUCTION

Mood disorders are some of the most prevalent neuropsychiatric disorders and are characterized by disturbances not only in mood, but also in cognition, sleep and psychosocial functioning, and can be associated with suicide. Pharmacological interventions, psychotherapy, or a combination of both, form the basic approach to the treatment of mood disorders. The monoamine hypothesis of depression, formulated during the 1960s, has made a tremendous contribution to understanding the pathophysiology of mood disorders, as well as to the development of antidepressants; every known antidepressant drug acts on one or more of the three monoamines – serotonin, norepinephrine and dopamine. Although current antidepressants can dramatically improve the outcome of major depressive disorder, the available medications have many shortcomings, resulting in a significant unmet need for patients. For example, only a minority of patients experience complete remission after treatment with conventional antidepressants, and many patients relapse, in additional to experiencing unacceptable side effects (1). Thus, there remains a need for antidepressants with efficacy in a broader group of depressed patients that also exhibit improved tolerability and reduced side effects. Targets other than the monoamine system might therefore yield antidepressant drugs with these features, a theory that has led to the search for novel antidepressant mechanisms.

Recent findings emerging from a variety of research fields have shed light on the importance of intracellular targets in the pathogenesis/pathophysiology of mood disorders, as well as in the therapeutic action of antidepressants (1-4). Therefore, drugs acting on these targets should be considered reasonable candidates for a new generation of antidepressant molecules. Recent proteomics studies demonstrated, for example, that drugs acting on a plasma membrane receptor can alter hundreds of pathways downstream of the receptor (5). Drugs targeting a specific intracellular target therefore have potential as antidepressants with novel mechanisms, and thus with a different efficacy and tolerability profile than current antidepressants targeting monoamine systems. In fact, current antidepressants have been repeatedly reported to affect the activities of intracellular targets and gene expression independently of their action

on the monoaminergic system, suggesting that their pharmacological effects may partly rely on their actions on as-yet-unidentified intracellular targets (6, 7). Furthermore, it is well known that different selective serotonin reuptake inhibitors (SSRIs) often show different pharmacological profiles in the treatment of psychiatric disorders (1). Thus, examining in detail the pharmacological action of conventional antidepressants may provide another approach for identifying novel targets for the next generation of antidepressants by focusing on intracellular targets.

The σ receptor has long been expected to serve as a novel target for psychotherapeutic drugs. Although originally proposed as a subtype of opioid receptors and implicated in schizophrenia, a series of recent studies confirm that the σ receptor is a nonopioid endoplasmic reticulum (ER) protein involved in a variety of brain functions (8, 9). It is currently accepted that σ receptors are classified in at least two subtypes — σ_1 and σ_2 (10). Growing evidence indicates potential cognition-enhancing and antidepressant-like actions for σ_1 agonists (11). Together with recent extensive characterization of the molecular function of σ receptors, these findings led the research community to evaluate the potential of σ receptors as targets for antidepressant action (Fig. 1). Furthermore, recent studies have indicated that the binding affinity of some current antidepressants for σ_1 receptors may play a role in their therapeutic action. In this review, we focus in particular on the σ_1 subtype, and discuss the potential of σ_1 ligands as novel therapeutic agents for the treatment of mood disorders.

STRUCTURE AND LOCALIZATION OF THE σ_1 RECEPTOR

Although the binding site for σ_1 ligands was extensively characterized during the 1980s and 1990s (12), the amino acid sequence and the structure of the σ_1 receptor have only just begun to be unveiled. (The structure of the σ_2 receptor is still unknown.) The σ_1 receptor is a 24-kDa protein mainly localized at the ER (13). It is an integral membrane protein with two transmembrane domains and a long *C*-terminus in the lumen of the ER (Fig. 2A) (14). It is assumed that the double-arginine sequence (–RR–) at the *N*-terminus retains σ_1 receptors at the ER membrane (15). The results of recent studies demonstrated that σ_1 receptors are particularly enriched at the ER subdomain apposed to mitochondria – the mitochondria-associated ER membrane (MAM). Thus, σ_1 receptors are positioned to regulate the crosstalk of signals between ER and mitochondria (Fig. 2B) (14). Under cellular stress (e.g., heat shock or glucose deprivation), however, σ_1 receptors are highly dynamic (14, 16) and can translocate from the ER membrane to loci in the vicinity of the plasma membrane (i.e., plasmalemma; see Fig. 2B).

The σ_1 receptors are expressed in the brain in addition to many other organs, including spinal cord, liver, pancreas, adrenal grand and lung (13, 17). It has also been shown that σ_1 receptors are highly expressed in various cancer cells (18). Recent research has sought to exploit this characteristic in order to develop σ ligands as tracers for cancer diagnosis, as well as cancer therapies (19). In the brain, σ_1

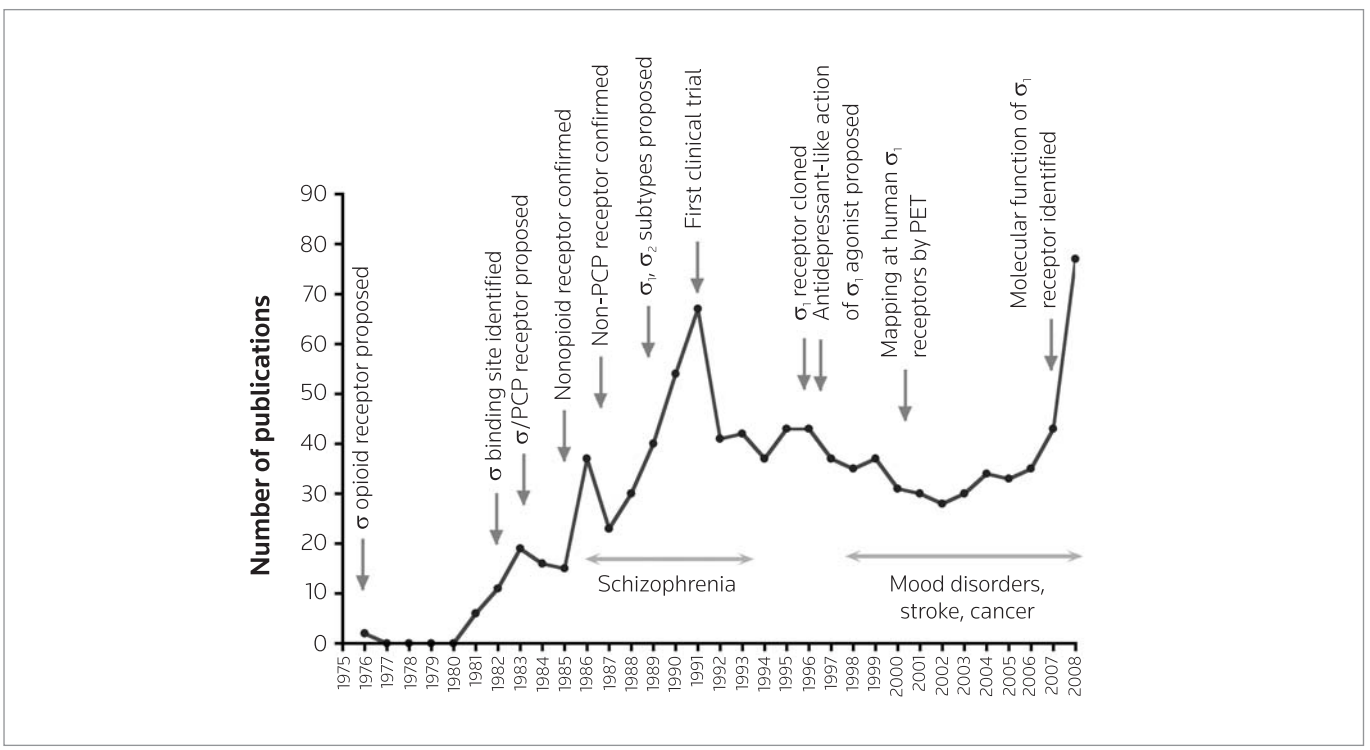

Figure 1. The history of σ receptor research. Publications related to σ receptors were searched using the National Library of Medicine's PubMed literature database. Only studies with the main focus on σ receptors were counted. Up until the mid-1990s, the primary clinical target of σ ligands was schizophrenia, but this focus later shifted to targeting mood disorders and strokes in the CNS field, in addition to cancers in the oncology field. The structure, molecular functions, distribution and pharmacology of the σ_1 receptor remained an enigma during the 1980s-1990s; however, recent findings from different research fields have begun to elucidate these features, resulting in a greater understanding of the clinical implications of targeting the σ_1 receptor, and leading the research field to its later stage (2000–).

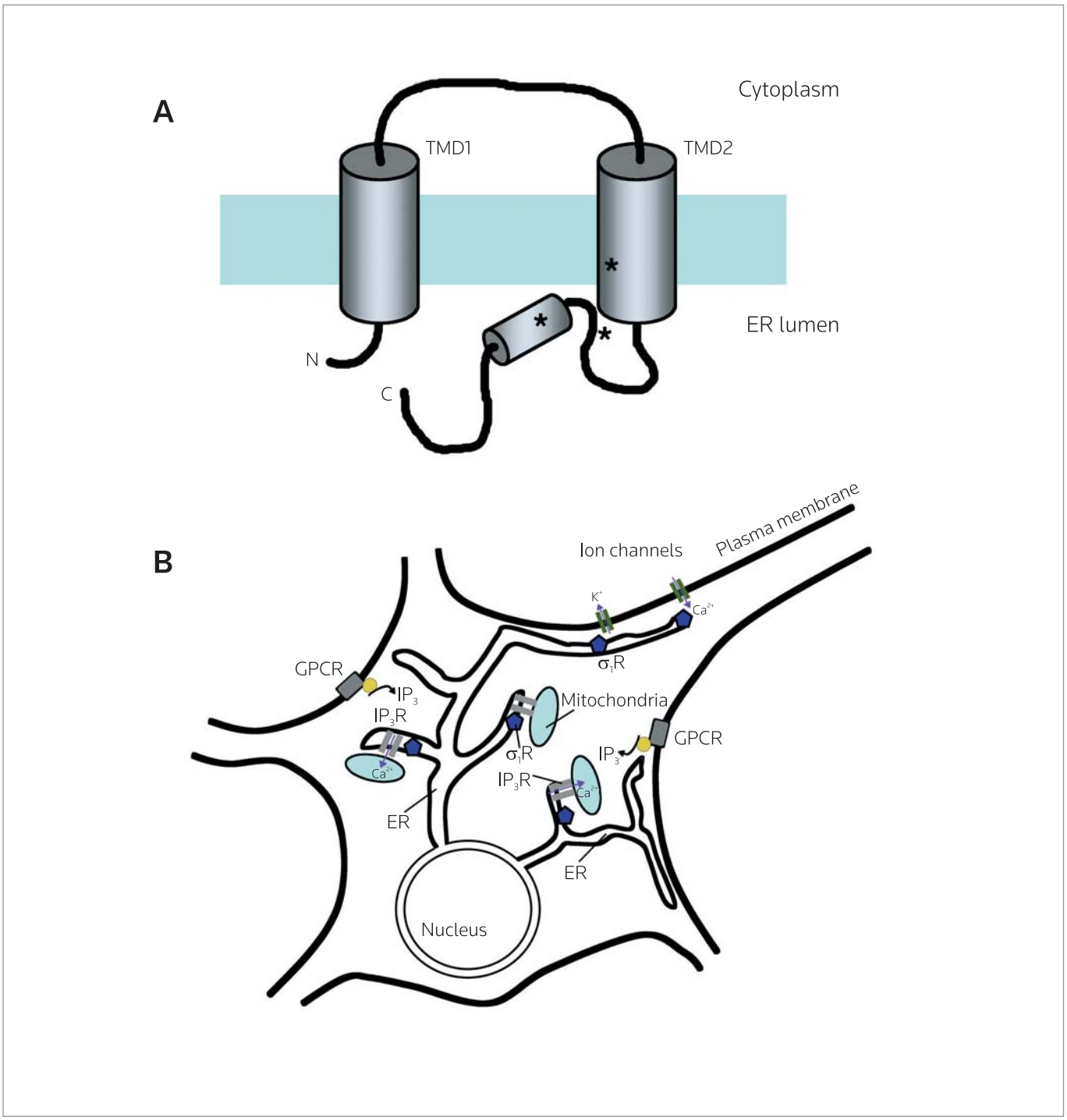

Figure 2. Structure, localization and function of the σ_1 receptor. **A**. Membrane structure of the σ_1 receptor. Sigma-1 receptors are mainly localized at the endoplasmic reticulum (ER) membrane and possess two transmembrane domains (TMD). The *C*-terminus of the σ_1 receptor residing in the lumen of the ER contains chaperone activity. *Indicates the domains responsible for formation of the putative ligand binding site. **B**. Cellular localization and function of the σ_1 receptor. Sigma-1 receptors (indicated by a blue pentagon) are intracellular molecules particularly enriched at ER subdomains associated with mitochondria (the mitochondria-associated ER membrane, MAM). Inositol 1,4,5-trisphosphate (IP_3) generated upon activation of G protein-coupled receptors (GPCRs) activates IP_3 receptors at the ER. Upon activation, IP_3 receptors at the MAM supply Ca^{2+} to mitochondria, leading to potentiation of the tricarboxylic acid (TCA) cycle and energy production in mitochondria. On the other hand, IP_3 receptors at the bulk ER membrane (not depicted here) mainly supply Ca^{2+} to the cytosol. Sigma-1 receptors as molecular chaperones associate with IP_3 receptors at the MAM to stabilize the latter and ensure proper Ca^{2+} transmission from the MAM to mitochondria. Sigma-1 receptors under certain cellular conditions translocate on the ER to the plasmalemma. Recent studies suggest that σ_1 receptors can regulate various ion channels at the plasma membrane.

receptors show a discrete distribution pattern, with high expression in the hippocampus, amygdala, locus coeruleus, red nucleus, frontal cortex and substantia nigra (20). This regional specificity matches well with the hypothesized role of σ_1 receptors in memory, cognition, emotion and motor functions (8, 21, 22). Work using recently established σ_1 receptor knockout mice will help further clarify the brain region(s) involved in σ_1 expression, and the related behavioral and psychological events that are under tight regulation by σ_1 receptors.

SIGMA-1 RECEPTOR: A NOVEL LIGAND-OPERATED MOLECULAR CHAPERONE

Molecular chaperones as therapeutic targets

The 3D structure of a protein that results from correct polypeptide folding is essential to its normal function. Molecular chaperones (also known as stress proteins) are defined as proteins that regulate the folding status of a spectrum of proteins and can stabilize the conformation of proteins and/or correct the folding status of unfolded or misfolded proteins. Molecular chaperones fall into a few subclasses, namely heat shock proteins (HSP; e.g., HSP70, BiP), lectin-type chaperones for glycoproteins (e.g., calnexin, calreticulin) and foldases (e.g., disulfide isomerases) (23). Because the ER is the major cellular factory synthesizing most proteins of the cell, this organelle is greatly enriched with molecular chaperones.

When the activity of molecular chaperones is compromised, or the amount of misfolded protein in a cell is beyond the capacity of the molecular chaperones to process, proteins begin to form highly toxic aggregates, leading to cellular dysfunction or apoptosis (23). Human diseases caused by protein misfolding/aggregates are collectively called "conformational diseases", and include Parkinson's disease, Alzheimer's disease and type 2 diabetes (24). Results from recent studies suggest the possible involvement of cellular stress or ER stress in mood disorders as well (1, 25-27). Here, "cellular stress" is defined as stimuli that result in the formation of misfolded proteins, which when concentrated in the ER is known as "ER stress". Because several diseases are caused by protein misfolding and aggregates, molecular chaperones are expected to serve as therapeutic targets for drugs. Unfortunately, it has proved difficult to synthesize compounds that activate or inhibit the function of molecular chaperones; nevertheless, an inhibitor of the heat shock protein HSP90 has recently been synthesized and introduced into clinical trials for the potential treatment of cancer (28).

The σ_1 receptor as a molecular chaperone

A study recently identified the σ_1 receptor as a novel ER chaperone. The ER lumenal domain of the σ_1 receptor possesses robust chaperone activity that prevents the aggregation of a variety of proteins in vitro and has been shown to stabilize the ER Ca^{2+} channel inositol 1,4,5-trisphisphate (IP_3) receptor in vivo. The IP_3 receptor is an important molecule for initiating intracellular Ca^{2+} signaling downstream of G_q protein-coupled receptors. IP_3 generated upon activation of metabotropic receptors leads to Ca^{2+} efflux from the ER to the cytoplasm/mitochondria via IP_3 receptors. It should be noted that σ_1 receptors are predominantly expressed at the MAM, thereby regulating the IP_3 receptor-mediated Ca^{2+} influx from the ER to the mitochondria (14). Because mitochondrial Ca^{2+} originating from the ER is a key activator of three dehydrogenases in the tricarboxylic acid (TCA) cycle (29-31), the σ_1 receptor is assumed to serve as a regulator of ATP production and bioenergetics within the cell.

A unique characteristic of the σ_1 receptor is its ligand-operated mechanism for regulating activation/inactivation of its chaperone activity, as demonstrated in studies carried out in Chinese hamster ovary (CHO) cells. The inactive σ_1 receptor forms a protein complex with BiP, an ER-specific homologue of HSP. Binding of σ_1 agonists and certain cations can promote the dissociation of σ_1 receptors from BiP, thus activating the chaperone function of the σ_1 receptor (14). Certain psychotropic drugs, including antidepressants and neurosteroids, activate σ_1 receptors in this way, whereas haloperidol and progesterone block the action of σ_1 agonists by tightening the association between the σ_1 receptor and BiP (Fig. 3). The basic molecular mechanism of the σ_1 receptor must be tested in the nervous system for further confirmation and clarification. Nevertheless, experimental evidence to date suggests that the unique "receptor chaperone" property has great potential for being exploited by future therapeutics.

The σ_1 receptors regulate various ion channels, including K^+, Ca^{2+} and Cl^- channels, NMDA receptors, the release of various neurotransmitters, lipid transport, brain-derived neurotrophic factor (BDNF) signaling, myelination, neuritogenesis and synaptogenesis (7, 18, 32-39), as shown in Table I. It is unclear at present how the chaperone activity of σ_1 receptors contributes to the diverse physiological actions of the receptor. As σ_1 receptors are dynamic, moving from the ER to the plasmalemma (16), the action of the receptor may not necessarily be restricted to the MAM, especially under cellular stress. Although the majority of σ_1 receptors localize at the ER, σ_1 receptors can also regulate presynaptic and/or postsynaptic proteins at the plasma membrane. Because any antidepressant-like action should essentially involve the alteration of neuronal activity, the regulation of various ion channels by the σ_1 receptor is of particular interest for future investigations into the activity of this receptor. The σ_1 receptors tonically inhibit ion channels involved in both neuronal excitation and inhibition (38, 40). One line of evidence suggests that activation of σ_1 receptors does not merely cause hyper- or hypoactivation of neuronal activity, but rather normalizes ion dynamics in neurons (41).

SIGMA-1 RECEPTOR LIGANDS

Clinically used drugs that bind to the σ_1 receptor

Structurally diverse compounds including antipsychotics, antidepressants, benzomorphans and neurosteroids bind to σ_1 receptors (42-44). Among clinically used drugs, butyrophenone derivatives, especially haloperidol (K_i = 4 nM), have the highest affinity for the σ_1 receptor. Although tricyclic antidepressants (e.g., imipramine) possess moderate affinities for σ_1 receptors, SSRIs generally have higher affinities, with a few exceptions. Among SSRIs, fluvoxamine has the highest affinity for σ_1 receptors (K_i = 36 nM) (45).

Although the pharmacological/biological relevance of the σ_1 receptor-binding capability of these psychotropic drugs has not yet been fully clarified, recent evidence supports the possibility that activa-

	Agonist (activation)	Antagonist (inactivation)	No effect
			
Cation	K^+ Mg^{2+}	Ca^{2+} Mn^{2+}	Na^+ Li^+
Neurosteroids	Pregnenolone-S DHEA-S	Progesterone	Estradiol
Synthetic compounds	(+)-Pentazocine (+)-SKF-10047 Fluvoxamine Imipramine	Haloperidol NE-100	Methamphetamine

Figure 3. Mode of action of the receptor chaperone. The σ_1 receptor chaperone in the dormant state forms a protein complex with another endoplasmic reticulum (ER) chaperone, BiP. Sigma-1 agonists or cations such as potassium or magnesium activate the chaperone activity of the σ_1 receptor. Pregnenolone-S, pregnenolone sulfate; DHEA-S, dehydroepiandrosterone sulfate.

Table I. *Functions of the σ_1 receptor in the nervous system.*

Molecular level
ER chaperone
Ameliorating endoplasmic reticulum stress Inhibition of protein misfolding and degradation Inhibition of apoptosis
Physiological level
Regulation of signal transduction
Ca^{2+} signaling via IP_3 receptors Regulation of ion channels (e.g., K^+ channels, NMDA receptor) Regulation of neurotransmitters (e.g., dopamine, serotonin) Regulation of trophic factor signaling (e.g., BDNF, NGF, EGF)
Cellular differentiation
Neuritogenesis Synaptogenesis Myelination
Long-term potentiation
Neuroprotection
Inhibition of ischemic infarction Inhibition of β-amyloid-induced neurodegeneration
Pain
Antinociceptive effect of antagonists

Table II. *Psychotropic drugs with actions on σ_1 receptors.*

Agonist	Antagonist
Pentazocine	Haloperidol
Dextromethorphan	Progesterone
Fluvoxamine	Sertraline
Imipramine	
Amantadine	
Donepezil	
Opipramol	
Dehydroepiandrosterone sulfate	
Pregnenolone sulfate	
Hyperforin/hypericin	

tion of the σ_1 receptor is responsible for some of their pharmacological actions. For example, the agonist imipramine and certain SSRIs promote the dissociation of σ_1 receptors from BiP, resulting in activation of the σ_1 receptor chaperone. Haloperidol antagonizes the action of agonists in the same system (Fig. 3). Fluvoxamine potentiates neuritogenesis of nerve growth factor (NGF)-treated PC-12 cells via σ_1 receptors, an action that is blocked by the selective σ_1 antagonist NE-100 (7, 46). Fluvoxamine has also been shown to improve phencyclidine (PCP)-induced cognitive impairment in animals via activation of σ_1 receptors (47). A recent PET study demonstrated that a single oral administration of fluvoxamine (50-200 mg) can displace the binding of the selective σ_1 agonist [^{11}C]-cutamesine in human brain (48).

Pharmacophore and binding site of σ_1 ligands

One of the goals of σ receptor research is to develop highly selective ligands with a view to introducing them into the clinical setting. To this end, detailed characterization of the ligand binding site of the σ_1 receptor, as well as the pharmacophore of the ligands, is essential. The mechanism underlying the unique binding property of σ_1 receptors has been extensively examined. One line of evidence suggests a unique structural configuration of the ligand binding site of the σ_1 receptor; in this model the second transmembrane domain and a few charged amino acids at the ER lumenal domain constitute the putative ligand binding pocket (Fig. 2A) (49-51). Thus, the ligand

binding pocket is supposed to contain both highly hydrophobic and hydrophilic amino acids, perhaps making the pocket favorable for binding a wide spectrum of hydrophobic or amphiphilic compounds. This intramolecular configuration is also speculated to contribute to the association between the σ_1 receptor and BiP (9, 14).

A number of studies have been conducted to identify the pharmacophore of σ_1 ligands (52, 53). Dissimilar σ_1 ligands often consist of an amine site flanked by two hydrophobic regions. Selective σ_1 ligands with a picomolar range of affinity were recently synthesized (54). Details of the ligand structures are summarized in recent comprehensive reviews (55, 56).

ANTIDEPRESSANT-LIKE ACTION OF σ_1 AGONISTS

Evidence from preclinical studies

Research findings such as the elucidation of the σ receptor binding profile of haloperidol and the discovery of the psychotomimetic action of σ-binding benzomorphans have provoked great interest in exploring novel antipsychotic drugs (57, 58), and initial research into σ ligands was aimed at schizophrenia and drug dependence as clinical targets (Fig. 1). However, newly synthesized selective σ_1 ligands often failed to show an effect on the locomotor activity of animals (42). Furthermore, their effects on psychostimulant-induced hyperlocomotion were inconclusive and often contradictory (59-61).

In the late 1990s, a new research angle emerged following a few interesting findings demonstrating antiamnesic and antidepressant-like actions of σ_1 ligands. In the first study demonstrating the antidepressant-like action of σ_1 agonists, cutamesine (SA-4503) was shown to decrease immobility time in the forced swimming test without any effect on open-field locomotion (60). Interestingly, this effect was achieved following a single administration of the drug (thereby differing from imipramine, which requires chronic administration to exert an equivalent effect). The "rapid" antidepressant-like action of σ_1 agonists has been replicated by different research teams with different ligands (62, 63). In addition to behavioral studies, electrophysiological studies demonstrated a rapid antidepressant-like action for σ_1 agonists (64, 65). It is well documented that the acute administration of classic antidepressants depresses the firing rate of dorsal raphe 5-HT neurons, whereas chronic use (> 5 days) recovers the firing rate, leading to enhancement of 5-HT release. The latter action is assumed to constitute the therapeutic action of antidepressants. Selective σ_1 agonists, in contrast to classic antidepressants, were shown to potentiate 5-HT neuronal firing within 2 days of administration (65).

Another interesting pharmacological property of σ_1 receptors is their action as "modulators" or "amplifiers" of monoaminergic or glutamatergic signal transmission (42, 66). Agonists do not exert pharmacological effects in animals or in vitro systems per se, but modulate physiological or behavioral responses induced by activation/inhibition of glutamatergic (NMDA receptors), serotonergic and dopaminergic systems (64). When a σ_1 agonist is combined with a 5-HT_{1A} receptor agonist, the anti-immobility effect in the forced swimming test is synergistically potentiated (67). Compounds possessing agonist properties at both σ_1 receptors and receptors in other systems (e.g., 5-HT_{1A} and muscarinic acetylcholine receptors) exert antidepressant-like or antiamnesic actions at reduced doses compared with agents having affinity for only one receptor (67, 68). As some currently used antidepressant drugs act on both σ receptors and monoaminergic systems, it is important to revisit the pharmacological profiles of such drugs, paying greater attention to their affinities for the σ_1 receptor and monoaminergic receptors/transporters.

Sigma-1 receptor knockout mice are now available for preclinical research. Homozygous mutant mice lacking σ_1 receptors are viable, fertile and show no apparent overt phenotype in muscular or skeletal development. However, the mice show slightly reduced spontaneous locomotor activity and are less responsive to the σ_1 receptor agonist SKF-10047, which induces hyperlocomotion in wild-type mice (69). Importantly, the knockout mice, similar to wild-type mice, show hyperlocomotion upon administration of methamphetamine (70). A recent study demonstrates that σ_1 receptor knockout mice show longer immobility time in the forced swimming test, indicative of the depression-like phenotype of the mice (71).

Neurosteroids and σ_1 receptors

Some neurosteroids, such as progesterone, pregnenolone sulfate and dehydroepiandrosterone sulfate (DHEA-S), bind to σ_1 receptors (42). In in vitro studies, neuroactive steroids have been shown to promote the dissociation of σ_1 receptors from BiP, as well as the activation of neuronal differentiation via σ_1 receptors (14, 72). Results from animal studies have shown that neuroactive steroids improve learning and memory and exert antidepressant-like actions, at least in part via σ_1 receptors (11, 73, 74). Neurosteroids are thus considered to be one of the possible endogenous ligands for σ_1 receptors.

A range of studies suggest that the level of neurosteroids is reduced in the brains of patients suffering from affective disorders (74). For example, the content of alloprogesterone in the cerebrospinal fluid (CSF) is reduced in patients with major depression, but recovers following 8-10 weeks of treatment with fluoxetine or fluvoxamine, levels correlating significantly with improvements in clinical symptoms (75). Interestingly, the action of SSRIs on neurosteroid levels appears to be independent of their action on serotonin reuptake (76). Some other targets, such as $GABA_A$ receptors and σ_1 receptors, are proposed to have roles in the antidepressant-like action of neurosteroids and the novel action of SSRIs (75, 77).

Sigma-1 agonists as clinical antidepressants

As mentioned, a PET study demonstrated that fluvoxamine (K_i = 36 nM for σ_1 receptors) can occupy the receptors in the human brain (48). Although preclinical data support the pharmacological relevance of receptor occupancy with σ_1 ligands, the relevance for the treatment of human disease needs further clarification. Nevertheless, several clinical studies suggest the potential usefulness of σ_1 ligands in the treatment of psychiatric disorders. Although they failed in clinical trials to ameliorate the acute positive symptoms of schizophrenia, some σ ligands were shown to improve certain negative symptoms of chronic schizophrenia (78-82). Despite the fact that SSRIs share a common primary action at the 5-HT transporter, their pharmacological profiles in clinical settings are remarkably heterogeneous. Fluvoxamine shows superior efficacy in treating psychotic depression (83-85), a severe depressive condition accom-

panied by delusions that is often treated with electroconvulsive therapy and combinations of antipsychotics and antidepressants. However, the efficacy of various SSRIs in treating psychotic depression has been shown to correlate well with their affinities for the σ_1 receptor, but not those for the 5-HT transporter (84). It has also been reported that combination therapy with fluvoxamine and antipsychotic drugs improves the negative symptoms of schizophrenia, whereas the combination with the SSRI paroxetine does not (86).

Igmesine (JO-1784) was the first σ_1 ligand introduced into clinical trials for major depressive disorder. In a double-blind study in the U.K., igmesine produced significant improvement in depressive symptoms, although no significant efficacy was seen in Czech and Polish populations (82, 87) and Pfizer subsequently discontinued development of this drug candidate. Recently, cutamesine was tested in double-blind, randomized, placebo-controlled phase II clinical trials in major depressive disorder and post-stroke recovery (88).

In light of the neuroprotective action of σ_1 receptor agonists, as demonstrated in rat models of cerebral ischemia (89, 90), it would be interesting to examine the efficacy of σ_1 agonists in depressive patients with comorbid vascular and/or neurological problems. Furthermore, it is worthwhile to point out that σ_1 agonists have been shown to generally improve memory and cognition in preclinical studies (11). Systematic and extensive evaluation of cognitive function may be necessary to elucidate the precise effect of σ_1 agonists in clinical settings. Having a line of antidepressant drugs targeting the different subcomponents of depressive symptoms (cognitive impairment, anxiety, depressive mood, etc.) might be ideal, as this would enable physicians to tailor antidepressant treatments for individual patients.

CONCLUSIONS

Since being originally misconceptualized as a subtype of opioid receptor over 30 years ago, σ receptors have remained a mysterious and controversial entity. However, the molecular and physiological functions of the σ_1 receptor are now beginning to be unveiled. Sigma-1 receptors are ER proteins possessing an innate chaperone activity for stabilizing client proteins (14). They regulate neuronal survival, morphogenesis of neurons or glia (e.g., myelination, synaptogenesis), neuronal firing and the release of several neurotransmitters (7, 33, 36, 37, 64). Preclinical studies have demonstrated the antidepressant-like, antiamnesic and neuroprotective effects of σ_1 receptor agonists (43, 44, 89, 90), and findings from clinical studies indicate the possible usefulness of σ_1 ligands in the treatment of neuropsychiatric disorders, including mood disorders. However, several pressing questions regarding the clinical potential of the σ_1 receptor remain outstanding, including: 1) which symptoms – cognition, mood, anxiety or others – are the primary target of selective σ_1 ligands in humans; 2) whether the clinical effects of some antidepressants depend (in part) on synergistic effects at σ_1 and monoaminergic receptors; 3) how long might treatment with σ_1 agonists be required to exert any therapeutic effect; and 4) whether there are common side effects associated with the use of selective σ_1 agonists or antagonists. When these questions are answered, together with further clarification at the molecular level, the "sigma enigma" will finally be solved.

DISCLOSURE

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