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REVIEW

POTENTIAL ANTIDEPRESSANT ACTIVITY OF SIGMA LIGANDS

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Despite many years' studies of antidepressant drugs (ADs), their mechanism of action still remains unclear. Recently, it has been postulated that substances capable of reducing neurotransmission at the NMDA complex may represent a new class of ADs. Since several ADs have a high affinity for σ receptors, the σ binding site may be a relevant mechanism in antidepressant action. Moreover, σ ligands are able to modulate the activity of the central neurotransmitter systems, including noradrenergic, serotonergic, dopaminergic and glutamatergic (NMDA) ones, which are seemingly important for the mechanism of action of known ADs. The existence of at least two different subtypes of σ receptors, denoted σ_1 and σ_2 is now widely accepted. The selective agonists of both σ receptor subtypes are available at present. In particular, a potential antidepressant activity of σ_1 receptor agonists has been postulated, since the antidepressive-like actions of these compounds have been shown in animal models. This article reviews the findings related to potential antidepressant activity of new, selective σ ligands.

Key words: *sigma receptors, selective sigma ligands, antidepressant activity, animal models*

Introduction

The term sigma (σ) receptors was first proposed by Martin et al. [49] to explain, on the basis of *in vivo* experiments, the effects of benzomorphans, such as N-allyl-normetazocine (SKF 10,047), pentazocine and cyclazocine which induced a characteristic pattern of stimulation ("canine delirium"), differentiating these compounds from morphine-syndrome and ketocyclazocine- syndrome. Though initially the σ receptors were considered to be a type of opiate receptor (beside μ and κ), later studies (using more selective ligands and more precise techniques) convincingly demonstrated that this opinion was not true. Further investigations have revealed that levorotatory form of SKF 10,047 binds primarily to μ and κ opioid receptors, while its dextrorotatory analogue is distinguished by much higher affinity for σ site and considerable affinity for phencyclidine (PCP) receptor. For these reasons, Martin et al. [49], who used (±)-SKF 10,047, observed as well antinociceptive effects (resulting from the interaction with μ and κ opioid receptors mediated by (–)-SKF 10,047) as psychotomimetic symptoms, believed to be an effect of (+)-SKF 10,047 binding to PCP receptors, not reversed by an opiate antagonist, naloxone.

The lack of the selectivity shown by several compounds, including benzomorphans and PCP derivatives on the one hand, and similarities in biochemical and behavioral effects of some σ ligands and PCP on the other, suggested actions *via* the same receptor site, so-called "σ/PCP". Further results (including autoradiographic studies using more selective radioligands) demonstrated that σ and PCP receptors were distinct sites and their distribution in brain regions was found to differ [23, 48, 55, 66].

The use of nonselective ligands, including the prototypic agonist, N-allyl-normetazocine, to characterize σ receptors resulted in an accumulation of confusing and conflicting data which made the progress in this field more difficult. Table 1 presents differences in affinity of some ligands of σ and PCP receptor sites. These data indicate that (+)-SKF 10,047 shows 12.5 times higher affinity for σ receptor than its levorotatory analogue, whereas both forms exhibit the affinity for PCP receptor (dextrorotatory form is somewhat more potent) (Tab. 1). On the other hand, pentazocine, having comparable affinity for σ site, binds to PCP receptor to much lesser extent (5–8 times) [23].

Table 1. IC_{50} values for drugs competing with the [^{3}H]ligands for σ and phencyclidine (PCP) receptor binding sites (rat brain membranes)

Compound	IC_{50} (nM)		
	(+)-[^{3}H]SKF 10,047 + TCP*	(+)-[^{3}H]SKF 10,047 + haloperidol	[^{3}H]TCP
(+)-SKF 10,047	**55**	**320**	**405**
(–)-SKF 10,047	**690**	**530**	**820**
(+)-3-PPP	45	> 50000	> 50000
Haloperidol	8	> 50000	> 50000
TCP	8330	25	10
PCP	1450	48	66
Pentazocine	55	1520	3310

* 1-[1-(2-thienyl)cyclohexyl]piperidine. According to [23]

Characteristics and functions of σ receptor

The σ receptors have been labeled and visualized with various radioligands using autoradiographic procedures. The numerous data demonstrate that σ receptors are unevenly distributed in many brain areas and are quite abundant in various peripheral tissues (the kidneys, lungs, intestine, muscles, and, most of all, the liver). In the central nervous system, σ receptors are concentrated in brainstem areas, certain limbic structures, some predominantly sensory areas and brain regions associated with endocrine function [24, 55, 94].

Binding studies and *in vivo* or *in vitro* functional bioassays led to the distinction of at least two subpopulations of σ receptors, termed σ_1 and σ_2 [5, 34, 65]. This classification is mostly based on differences in binding of radioligands: σ_1 receptor is able to distinguish between spatial isomers, showing preference for dextrorotatory forms [(+)-pentazocine, (+)-SKF 10,047, dextrometorphan], whereas the levorotatory form of these compounds as well as haloperidol or 1,3-di-o-tolylguanidine (DTG) bind with high affinity also to the σ_2 receptors.The σ_1 sites are particularly concentrated in the hippocampal formation and other limbic areas (involved in cognition and emotion), thus, they are suggested to play an important role in etiology and therapy of psychiatric disorders [13, 35, 36, 52, 94]. On the other hand, the highest densities of σ_2 receptors

were revealed particularly in regions related to motor functions (e.g. the motor cortex area, cerebellum) supporting their possible involvement in the modulation of posture and movements induced by σ ligands [5, 94].

However, σ_2 binding sites are also likely to modulate emotional responses, since Lu 28-179, a new selective σ_2 receptor ligand, shows anxiolytic-like effects in mouse and rat black and white two-compartment box test, the rat social interaction test and the Vogel conflict test [71].

Binding to σ_1 receptor is allosterically modulated by phenytoin and sensitive to the modulatory effects of guanosine triphosphate (GTP) and pertussis toxin, which suggests its coupling to G proteins ($G_{i/o}$). It is thought that activation of σ_1 receptor implicates many second messenger cascades, including arachidonic acid cascade, protein kinase C translocation, modulation of the phosphorylation state of specific proteins in the brain and phosphatidyl inositol turnover [19, 26, 60, 94]. Moreover, an interaction between σ ligands and calcium channels has been suggested [see: 94]. The findings of Brent et al. [7] demonstrated that protein phosphorylation (dependent on extracellular Ca^{2+}) may be one of the important mechanisms through which σ ligands produce their effects.

The most commonly used selective σ_1 receptor ligand is (+)-pentazocine, although new, more selective compounds of this type have been synthesized in recent years (e.g. SA4503), while the DTG, mixed σ_1/σ_2 receptor agonist, has been used as σ_2 receptor ligand or radioligand (in the presence of (+)-pentazocine). As mentioned above, a selective σ_2 receptor ligand, siramesine, has been introduced recently [71, 86]. The σ receptor ligands used so far showed low selectivity for its two subpopulations and for other receptors, particularly dopamine receptors. For instance, haloperidol, a typical neuroleptic, shows high affinity particularly for σ_1 sites and relatively lower for σ_2 sites. On the other hand, the aforementioned compound DTG binds with comparable potency to both σ_1 and σ_2 receptor subtypes (Tab. 2). Interestingly, some neurosteroids (e.g. progesterone, testosterone) exhibit marked selectivity for σ_1 receptor [53, 91]. Progesterone was the most effective, inhibiting [^{3}H]SKF 10,047 the binding in the rat brain homogenate at nanomolar concentrations, while pregnenolone, dehydroepiandrosterone (DHEA) and testosterone effects were relatively weaker.

Table 2. Affinities of some compounds for σ_1 and σ_2 receptor sites in the rat brain membranes

Compound	K_d or K_i (nM)	
	σ_1	σ_2
Haloperidol	3.12 ± 0.23	55.0 ± 9.3
(+)-Pentazocine	4.59 ± 0.26	1,052 ± 30
(–)-Pentazocine	7.41 ± 1.65	42.5 ± 1.7
DTG	17.9 ± 5.0	22.2 ± 3.5
(+)-SKF 10,047	19.4 ± 4.6	2680 ± 444
Progesterone	24.6 ± 6.6	15700 ± 100
Testosteron	49.7 ± 11.7	> 50000
(–)-SKF 10,047	84.9 ± 10.7	1100 ± 170
Dextrometorphan	85.5 ± 8.5	15800 ± 700
Dizocilpine (MK-801)	47300 ± 3500	73600 ± 3300

According to [56]

An electrophysiological *in vivo* model for studies of selective σ receptor ligands has been proposed by Debonnel et al. [2, 12, 13, 59]. Numerous results from this laboratory demonstrated that several σ_1 ligands, e.g. (+)-pentazocine, when applied by microiontophoresis or administered *iv* at low doses, potentiated the neuronal response to N-methyl-D-aspartate (NMDA) in the CA_3 region of the rat dorsal hippocampus but did not modify kainate- nor quisqualate-induced activations. Only a few σ ligands, including NE-100 (*N,N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine) and haloperidol, did not modify NMDA-induced firing activity but suppressed the potentiation of NMDA response induced by σ agonists. Thus, they were denoted σ antagonists. Similarly to σ_1 ligands, σ_2 agonists also potentiate the NMDA response [12]. A majority of σ agonists tested thus far generate bell-shaped dose-response curves with respect to potentiation of NMDA response. It is worth emphasizing that this dose-response relationship seems characteristic of σ receptor ligands, and was observed in some behavioral models as well [12, 54]. Additionally, neuroactive steroids in nanomolar range also modulate the NMDA-mediated responses. DHEA potentiated the NMDA-evoked electrical activity of CA_3 hippocampal pyramidal neurons, as do σ_1 receptor agonists, that could be blocked by haloperidol or NE-100, as well as by progesterone [3].

Recently, the σ_1 receptor was purified and cloned from several species (guinea pig liver, human placental cell line and brain, from mouse kidney and brain and from rat brain) and completely sequenced, showing that this protein was unrelated to known transmitter receptors [e.g. 58, 77]. The σ_1 receptor is a low molecular weight protein (27 kDa) composed of 223 amino acids, and has a single, putative transmembrane segment anchored in the endoplasmic reticulum membrane. This is a unique protein, which does not show homology with any protein present in mammalian brain tissue. The studies using a polyclonal antibody technique revealed that the immunolocalization of σ_1 receptors is associated with the mitochondrial membranes and endoplasmic reticulum [58].

Functional effects attributed to σ_1 receptor include antipsychotic effects (NE-100, panamesine, E-5842) [25, 61,74], antagonistic action against cocaine- and amphetamine-induced excitation and sensitization, neuroprotection and prevention of experimentally evoked amnesia in animals [52, 54, 76, 98]. The two former effects may be due to the fact that, besides their well-documented interaction with NMDA system, the σ_1 agonists are able to modulate (directly or indirectly) the cholinergic neurotransmission. SA4503, DTG and (+)-SKF 10,047 (similarly to neurosteroids, e.g. pregnenolone sulfate) enhanced acetylcholine release in the rat brain cortex and hippocampus. Moreover, the σ_1 receptor ligands inhibited carbachol-induced phosphatidyl inositol turnover in the rat brain and nicotine-stimulated catecholamine release [see 53]. It is worth reminding that many neuroleptics, most of all haloperidol, are characterized by high affinity for σ receptor [33]. At present, the selective σ_1 receptor ligands, both agonists: (+)-pentazocine, SA4503 and an antagonist, NE-100, are available [51, 61].

Much less is known about σ_2 receptor. Contrary to σ_1, σ_2 receptor has not been cloned as yet but it is thought that its protein possesses similar molecular weight between 18–21 kDa. An authoradiographic study with σ_2 receptor radioligands revealed its highest densities in the cerebellum, motor cortex, and substantia nigra pars reticulata. As well localization as other experimental data (dystonias in rats after administration of σ receptor ligands into the red nucleus) indicate a potential of σ_2 receptor to contribute to regulation of motor functions [86, 94].

Moreover, recent reports have confirmed earlier suggestions that σ_2 ligands modulate the dopamine transporter (DAT). Activation of σ_2 receptors results in the regulation of DAT activity *via* a calcium- and protein kinase C-dependent signaling mechanism [14]. Because of the crucial role played by DAT in the mechanism of action of several drugs of abuse, it is possible that drugs with antagonistic activity at σ_2 receptors might be of value in treating drug abuse.

Potential antidepressant activity of σ ligands

Several lines of evidence suggest a possible relationship of σ receptors and psychosis, e.g. psychomimetic activity of benzomorphan derivatives exhibiting high affinity for σ receptors or high affinity of many neuroleptics (including haloperidol) for this receptors [33, 94]. Moreover, activities of dopaminergic neurons (especially in the substantia nigra and ventral tegmental area, VTA) are variously modified by the systemic administration of σ ligands [13, 21, 22, 30, 57].

A potential of σ receptors to be implicated in AD action started to be considered much later [2, 13, 28, 35]. Many findings implied that ADs, representing different chemical groups, e.g. iprindol (atypical AD), clorgyline (MAO-I) or sertraline (a selective serotonin reuptake inhibitor, so-called SSRI) inhibited binding of selective σ receptor radioligands in the mouse and rat brain homogenates [27, 28, 35]. In addition, fluvoxamine, maprotiline and opipramol (at nanomolar concentrations) showed high affinity for σ receptor [72]. A majority of 22 clinically active ADs inhibited [^{3}H]pentazocine binding to σ_1 receptor in the mice forebrain homogenate (IC_{50} = 0.1–10 μM) [see: 35]. Chronic AD administration also modulated the concentration of radioligand binding to σ receptors in different brain regions, usually down-regulated σ_1 receptors [see: 13, 78].

Though mechanism of AD action has been studied for many years, it remains unclear in detail and still new hypotheses are proposed. The first one, developed in the 1960s, was monoaminergic hypothesis, which linked mechanism of AD action to an increase in noradrenaline and/or serotonin level in the synaptic cleft, caused by inhibition of either monoamine reuptake or their metabolism after a single drug administration [8, 11, 75]. Accord-

ing to this hypothesis, depression would be an effect of deficient monoamine concentrations, and thereby reduced neurotransmission. Its core idea, viz. a relationship between antidepressant effect and facilitation of monoaminergic neurotransmission still remains valid, which has been supported by clinical studies. However, clinical experience indicates that a single administration of ADs it not enough to achieve therapeutic efficacy, thus, antidepressant effect is presumably a result of adaptive changes caused by long-term AD treatment.

The hypothesis of β-adrenoceptor down-regulation was the first proposal, that included the above observations. In the middle of the 1970s, Vetulani and Sulser [93] showed that repeated (but not single) AD administration reduced reactivity of noradrenergic cyclic AMP generating system in the limbic forebrain. This finding and other data accumulated within the next years were the basis of the hypothesis which was generally accepted, since the most of ADs (representing different mechanism of action) therapies with were found to reduce the cyclic AMP response or the density of β-adrenoceptors in the cerebral cortex [87, 92].

More or less at the same time, other theories were created and developed, including serotonin [9, 20, 31] or dopamine [37, 67, 95] hypotheses. The latter has been a focus of many studies conducted at our Institute [16, 17, 37, 39–42, 44, 45], which demonstrated that repeated treatment with almost all clinically active ADs activated the dopamine system by increasing responsiveness to stimulants, including dopamine. This finding was supported by biochemical studies, which revealed that AD treatments might increase the density of dopamine D_2 and D_3 receptors in the respective brain structures as well as raise the concentration of mRNA encoding dopamine D_2 receptors in the limbic structures of the rat brain [16, 17, 69].

The basis of glutamatergic (NMDA) hypothesis, which was developed in the 1990s, was the discovery of Skolnick et al. that NMDA receptor changes may be involved in the action of ADs [for review see: 79]. It was found that NMDA receptor antagonists (MK-801, CGP 37849, CGP 40116) decreased the immobility time in the tail suspension and in Porsolt's test as well as in the chronic mild stress (CMS) model [46, 47, 62, 63, 89]. On the other hand, repeated treatments with ADs down-regulated the strychnine-insensitive glycine receptors in neocortical membranes, as demonstrated by reduction of the potency of glycine to inhibit [^{3}H]-5,7-dichlorokynurenic acid binding [64]. This effect showed better correlation with clinical efficacy of ADs than Porsolt's test or β-adrenergic down-regulation. Moreover, a small clinical trial recently demonstrated that *iv* infusion of ketamine, an uncompetitive NMDA receptor antagonist, produced a long-lasting (days) antidepressive action [4].

In general, the Skolnick's hypothesis combines the two different treatment strategies: monoamine and glutamate/NMDA, to produce directly (e.g. NMDA receptor antagonists) or indirectly (by modulating other neurotransmitter systems or intracellular factors, e.g. BDNF) the same endpoint, i.e. reduction of the NMDA function [79, 80].

It is widely accepted that σ receptors are able to modulate the neuronal activity, especially the effects of monoaminergic neurons and hippocampal neuron activity. When applied with microiontophoresis, they were reported to increase dopaminergic neuron activity in the VTA. Serotonergic neurons in the raphe nucleus and noradrenergic neurons in the locus coeruleus were activated by σ ligands. In the hippocampus, σ receptors are thought to play a role in the modulation of the glutamatergic neurotransmission, *via* indirect modulation of the NMDA receptor [2, 12, 13, 59, 97]. The results using extracellular single-unit recordings from pyramidal neurons of CA_3 region of the rat dorsal hippocampus showed that selective σ ligands at low doses exert a potentiating effect on NMDA-induced neuronal activation [12]. Many data have focused on involvement of σ receptors in the modulation of the glutamatergic (NMDA) neurotransmission on the dopaminergic (particularly mesocorticolimbic) neurons [e.g. 21, 57]. In addition, radioligand binding data indicate the presence of a moderate density of σ receptors in limbic structures, e.g. hippocampus, amygdala, septum and frontal cortex. These findings may have an essential significance for potential antidepressant activity of σ ligands.

SA4503, the selective σ_1 receptor agonist

The compound SA4503 is the recently described, selective σ receptor ligand, characterized on the basis of biochemical *in vitro* experiments as its agonist [51]. Preliminary studies indicated that this compound decreased immobility time in tail

suspension test and in Porsolt's test in mice [50, 90]. Moreover, some authors reported that SA4503 attenuated the learning impairment induced by non-competitive NMDA receptor antagonists in different pharmacological models (spontaneous alternation, step-down and step-through type of passive avoidance tests) [54].

Biochemical studies demonstrated that SA4503 increased the level of dopamine and its metabolite, dihydroxyphenylacetic acid (DOPAC), in the rat frontal cortex (but not in the hippocampus, striatum, cerebellum, hypothalamus), which was inhibited by a selective σ_1 receptor antagonist, NE-100 [30]. The elevated accumulation of L-DOPA in the frontal cortex was also reported after blockade of DOPA decarboxylase activity by NSD-1015, suggesting a rise in dopamine turnover in this brain region [30]. On the other hand, electrophysiological studies demonstrated that repeated administration of SA4503 (once a day for 21 days) produced a significant increase in the number of spontaneously active VTA dopaminergic neurons, which was inhibited by NE-100 [57]. This alteration produced by SA4503 resembles that reported for clinically active ADs (e.g. paroxetine, fluoxetine, citalopram, desipramine). Some results suggested that SA4503, like DTG or (+)-pentazocine, facilitated the dopaminergic transmission in the frontal cortex, a brain area that is believed to play an important role in the pathophysiology of depression [e.g. 21, 22, 57].

As mentioned above, SA4503 decreased immobility time in the forced swimming test in mice and rats. Similar effects were observed after administration of (+)-pentazocine and DTG to mice and rats [50, 83]. Those antidepressant-like effects were antagonized by the σ_1 receptor antagonist, NE-100 [50]. Moreover, SA4503 exerts a synergistic effect with imipramine (either compound being used at doses inactive *per se*) in Porsolt's test [84]. A similar synergistic effect was observed after imipramine and other new potential antidepressants, e.g. pramipexole [43]. It is worth adding that DHEA sulfate and pregnenolone sulfate acting as σ_1 receptor agonists, induced a reduction of immobility time in the forced swimming test, which was reversed by NE-100, a σ_1 antagonist [91].

Our results show (Tab. 3) that similarly to a majority of ADs, repeated (but not acute) treatment with SA4503 increases amphetamine- and quinpirole- (but not 7-OH-DPAT)-induced hyperactivity

Table 3. Comparison between effects of SA4503, a selective σ_1 receptor agonist, and some antidepressant drugs (after their repeated administrations) in behavioral tests

Drug	Amphetamine-induced hyperactivity (rat)	Quinpirole-induced hyperactivity (rat)	7-OH-DPAT-induced hyperactivity (rat)	Apomorphine-induced stereotypy (rat)	Clonidine-induced aggressiveness (mouse)	Phenylephrine-induced hyperexploration (rat)
Imipramine	↑	↑	↑	–	↑	↑
Citalopram	↑	↑	↑	–	↑	↑
Milnacipran	↑	–	↑	–	↑	↑
SA4503	↑	↑	–	–	↑	↑

See [38, 82, 84]

Table 4. Comparison between effects of SA4503, a selective σ_1 receptor agonist, and some antidepressant drugs (after their repeated administrations) in biochemical tests (dopaminergic system)

Drug	Autoradiography			mRNA level (*in situ* hybridization)	
	[^{3}H]Raclopride (D_2/D_3 antagonist)	[^{3}H]Quinpirole (D_3/D_2 agonist)	[^{3}H]7-OH-DPA (D_3 agonist)	D_1	D_2
Venlafaxine (30)	–		(↑)	–	–
Milnacipran (30)	↑	↓	–	–	–
Reboxetine (30)	–	– (↓)	– (↓)	–	–
SA4503 (3)	–	–	–	↑	↓

See [38, 81]

in rats. The lack of influence on the amphetamine-induced stereotypy indicates that a pharmacokinetic interaction between SA4503 and D-amphetamine as well as involvement of the nigrostriatal dopamine system, may be excluded. Additionally, SA4503 given repeatedly, enhanced the effect of phenylephrine, an α_1-adrenoceptor agonist, and clonidine (stimulating the postsynaptic α_1-adrenoceptor at high dose) in behavioral models (hyperexploratory activity in rats and aggressiveness in mice, respectively) [82].

Summing up, enhancement of amphetamine- and quinpirole-induced locomotor hyperactivities, together with an increase in the behavioral effects of treatment with α_1-adrenoceptor agonists, may suggest that repeated treatment with SA4503 up-regulates D_2-mediated dopaminergic and α_1-adrenergic transmission, both these effects being important for clinical antidepressant activity [82, 84].

Biochemical studies show that repeated administration of typical ADs (e.g. imipramine, citalopram or mianserin) increases the binding (density and affinity) to D_2 and D_3 receptor in the respective brain structures, as well as the concentration of mRNA coding for dopamine D_2 receptors [16, 17, 40, 69], whereas newer ADs (venlafaxine, milnacipran, reboxetine) did not evoke such significant changes (Tab. 4). Both an increase, a decrease and a lack of any changes in the radioligand binging ([^{3}H]raclopride and [^{3}H]quinpirole) were observed, and the only statistically significant effect in comparison with the control group was obtained with milnacipran, while reboxetine showed only slight activity. SA4503, administered repeatedly, did not influence radioligand binding to D_2 and D_3 receptors. It should be noted that its effects on expression of mRNA coding for D_1 and D_2 receptors were different than responses to both classic (e.g. imipramine) and newer (milnacipran or reboxetine) ADs. SA4503 raised the concentration of mRNA coding for D_1 receptor (in the shell of the nucleus accumbens septi) and reduced D_2 mRNA level (in the striatum), whereas tricyclic ADs enhanced expression of mRNA coding for D_2 receptor [81] (or did not alter D_1 and D_2 mRNA level, as milnacipran or reboxetine did) [see: 38]. Further studies are required for precise elucidation of the above biochemical changes exerted by SA4503.

Our latest studies demonstrated that ADs administered in combination with amantadine, memantine or neramexan, uncompetitive NMDA receptor antagonists, showed positive interaction in the forced swimming test in rats [70]. This interaction is particularly interesting in the case of SSRI (e.g. fluoxetine), which did not show an antidepressant-like activity in this test carried out in accordance with the original method of Porsolt, when given alone [see: 6]. It should be emphasized that combinations of these drugs, administered according to the same experimental schedule, did not increase locomotor or exploratory activity.

The σ receptor ligands (SA4503, DTG) administered jointly with amantadine (all at inactive doses when given alone) showed antidepressant-like activity in rats [85]. It is noteworthy that both amantadine and memantine exhibit marked affinity for σ receptor [32]. Moreover, joint administration of SA4503 or DTG with CGP 37849, a competitive NMDA receptor antagonist, elicited positive interaction in Porsolt's test in rats [own unpublished data].

In recent years, a selective σ_2 receptor ligand, siramesine, has been introduced. It exhibited anxiolytic potential (social interaction test, Vogel's test) and moderate antidepressant activity in CMS model [71, 73]. Siramesine neither *per se* affected activity of rats in Porsolt's test nor did it show any activity after combined administration with imipramine. However, its co-administration with amantadine decreased the immobility time in the forced swimming test, but only at one dose (the same as that active in CMS test) [85]. The above-described and some previous results indicate that activation of σ (particularly σ_1) receptor may be one of possible mechanisms by which drugs induce an antidepressant-like activity in the Porsolt's test and that this effect is enhanced by NMDA receptor antagonists. Thus, σ receptors may be involved in the behavioral responses in depression.

Other new σ ligands with potential antidepressant activity

Igmesine (JO1783)

Igmesine (JO1783) has been used as σ receptor ligand in different studies (electrophysiological, behavioral, biochemical). It is now known that it exhibits high selectivity for σ_1 receptors (IC_{50} for σ_2 receptor is > 1000 nM). Igmesine administered repeatedly (once a day for 21 days) induced a number of interesting changes, e.g. significant decrease in the binding density of β-adrenergic receptors (al-

though it does not bind to these receptors), thereby resembling most of ADs. Moreover, igmesine increased noradrenaline release in the rat prefrontal cortex (as measured by microdialysis) and decreased tyrosine hydroxylase activity after its repeated treatment [10].

Although igmesine does not directly interact with serotonin receptors, upon repeated treatment schedule, it augmented serotonin release, measured with microdialysis in the rat prefrontal cortex [10].

Like imipramine or many σ receptor ligands, igmesine inhibited the NMDA-induced increase in cGMP level in the rat cerebellum slices [1, 68, 94, 96]. This effect can result from igmesine influence on nitric oxide synthase activity, which was demonstrated for some other σ receptor ligands [18]. This pathway appears highly probable as one of possible ways in which σ ligands can modulate activity of NMDA receptor complex.

OPC-14523

In vitro studies have demonstrated that OPC-14523 at nanomolar concentrations binds to σ receptor (to both its subtypes to similar degree), and to 5-HT_{1A} receptor [29, 88]. Moreover, it might block the serotonin transporter *in vivo* and suppress its reuptake but this effect appears to be insufficient to mediate the acute antidepressant-like activity. Investigations of Tottori et al. [88] suggest that OPC-14523 action in the forced swimming test appeared earlier than after fluoxetine and even imipramine, since it could be observed already after a single dose of this compound (with lack of influence on basic locomotor activity). The 5-HT_{1A} receptor agonists, e.g. 8-OH-DPAT, induce rapid and effective antidepressant-like action in the forced swimming test [e.g. 15]. OPC-14523-induced decrease in immobility time in this test in mice and rats was antagonized both by NE-100, a σ_1 receptor antagonist, and by 5-HT_{1A} receptor antagonist, WAY-100635 [88].

It seems that unique mechanism of action of OPC-14523, combining antagonism at 5-HT_{1A} and σ receptors, amplifies its antidepressant potential and can manifest itself as quicker and more efficient clinical effect.

Summary and conclusions

In almost 30-year history of σ ligand research, investigations sometimes encountered difficulties and were periodically abandoned, which was mostly caused by a lack of appropriate tools and methods. As was demonstrated by recent findings, σ receptor is a unique protein, distinct from any known mammalian receptors. This property can indicate that mechanism underlying σ receptor function is also different. One of the possibilities is that the intracellular σ_1 receptor regulates several components implicated in plasma membrane related signal transduction.

Though the physiological role of these receptors still remains unclear, their well-documented interaction with NMDA system is worth recognition, as NMDA receptor complex is known to play an important role in neurodegenerative processes, learning and memory, and, according to glutamatergic theory, in the pathomechanism of depression.

Discovery that some neurosteroids exhibit marked affinity for σ receptors is another interesting finding of recent years. Among steroids, progesterone has the highest affinity for the σ_1 receptor and its physiological concentrations in brain and plasma may be sufficient to allow for a significant interaction with σ_1 sites. These data suggest that neurosteroids can be an important link in the mechanism of action of σ receptor ligands, and they can play a role of their endogenous ligands (e.g. progesterone for σ_1 receptor).

In spite of many unknowns still awaiting clarification, the recently introduced selective σ_1 and σ_2 receptor ligands not only can contribute to understanding of a role and mechanism essential for function of these receptors but also they have a potential to be used in the treatment of various diseases of the central nervous system, e.g. as antiamnesic, antipsychotic or antidepressant drugs.

REFERENCES

1. Akunne H.C., Zoski K.T., Whetzel S.Z., Cordon J.J., Brandon R.M., Roman F., Pugsley T.A.: Neuropharmacological profile of a selective sigma ligand, igmesine: a potential antidepressant. Neuropharmacology, 2001, 41, 138–149.
2. Bergeron R., Debonnel G., de Montigny C.: Modification of the NMDA response by antidepressant σ-receptor ligands. Eur. J. Pharmacol., 1993, 240, 319–323.
3. Bergeron R., de Montigny C., Debonnel G.: Potentiation of neuronal NMDA response induced by dehydroepiandrosterone and its suppression by progesterone: effects mediated via σ receptors. J. Neurosci., 1996, 16, 1193–1202.

4. Berman R.M., Cappiello A., Anand A., Oren D.A., Heninger G.R., Charney D.S., Krystal J.H.: Antidepressant effects of ketamine in depressed patients. Biol. Psychiat., 2000, 47, 351–354.
5. Bouchard P., Quirion R.: [^{3}H]1,3-Di(2-tolyl)guanidine and [^{3}H](+)pentazocine binding sites in the rat brain: autoradiographic visualization of the putative sigma$_1$ and sigma$_2$ receptor subtypes. Neuroscience, 1997, 76, 467–477.
6. Borsini F., Meli A.: Is the forced swimming test a suitable model for revealing antidepressant activity? Psychopharmacology, 1988, 94, 147–160.
7. Brent P.J., Herd L., Saunders H., Sim A.T.R., Dunkley P.R.: Protein phosphorylation and calcium uptake into rat forebrain synaptosomes: modulation by the σ-ligand, 1,3-ditolylguanidine. J. Neurochem., 1997, 68, 2201–2211.
8. Bunney W.E., Davis J.M.: Norepinephrine in depressive reactions. Arch. Gen. Psychiat., 1965, 13, 483–494.
9. Christensen A.V., Fjalland B., Pedersen V., Danneskiold-Samsoe P., Svendsen O.: Pharmacology of the new phthalane (Lu 10-171), with specific 5-HT uptake inhibiting properties. Eur. J. Pharmacol., 1977, 41, 153–162.
10. Cooke L.W., Acharya A.J., Davis M.D.: The effects of sigma$_1$ ligand, igmesine, on neurotransmitter activity in the rat as assessed by intracerebral microdialysis. Soc. Neurosci. Abstr., 1998, 24, Part 2, 583, 14.
11. Coppen A.J.: Biochemical aspects of depression. Int. Psychiat. Clin., 1969, 6, 53–81.
12. Couture S., Debonnel G.: Modulation of the neuronal response to N-methyl-D-aspartate by selective sigma$_2$ ligands. Synapse, 1998, 29, 62–71.
13. Debonnel G., de Montigny C.: Modulation of NMDA and dopaminergic neurotransmissions by sigma ligands: possible implications for the treatment of psychiatric disorders. Life Sci., 1996, 58, 721–734.
14. Derbez A.E., Mody R.M., Werling L.L.: Sigma(2)-receptor regulation of dopamine transporter via activation of protein kinase C. J. Pharmacol. Exp. Ther., 2002, 301, 306–314.
15. Detke M.J., Wieland S., Lucki I.: Blockade of the antidepressant-like effects of 8-OH-DPAT, buspirone and desipramine in the rat forced swim test by 5-HT$_{1A}$ receptor antagonists. Psychopharmacology, 1995, 119, 47–54.
16. Dziedzicka-Wasylewska M., Rogoż R., Klimek V., Maj J.: Repeated treatment of antidepressant drugs affects the levels of mRNA coding for D-1 and D-2 dopamine receptors in the rat brain. J. Neural Transm., 1997, 104, 515–524.
17. Dziedzicka-Wasylewska M., Rogóż Z., Skuza G., Dlaboga D., Maj J.: Effect of repeated treatment with tianeptine and fluoxetine on central dopamine D$_2$/D$_3$ receptors. Behav. Pharmacol., 2002, 13, 127–138.
18. Earley B., Canney M., Clune B., Caldwell M., Leonard B.E., Junien J.-L.: The effects of MK-801, ifenprodil, JO 1784, JO 1994 and JO 1997 on PK 11195 receptor binding, nitric oxide synthase (NO synthase) activity and infarct volume in a mouse model of focal cerebral ischaemia. Neurochem. Int., 1996, 28, 509–521.
19. Ferris C.D., Hirsh D.J., Brooks B.P., Snyder S.H.: Sigma receptors: from molecule to man. J. Neurochem., 1991, 57, 729–737.
20. Fuller R.W., Perry K.W., Molloy B.B.: Effect of an uptake inhibitor on serotonin metabolism in rat brain: studies with 3-(*p*-tri-fluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine (Lilly 110140). Life Sci., 1974, 15, 1161–1171.
21. Gronier B., Debonnel G.: Involvement of σ receptors in the modulation of the glutamatergic/NMDA neurotransmission in the dopaminergic systems. Eur. J. Pharmacol., 1999, 368, 183–196.
22. Gudelsky G.A.: Effects of σ receptor ligands on extracellular concentration of dopamine in the striatum and prefrontal cortex of the rat. Eur. J. Pharmacol., 1995, 286, 223–228.
23. Gundlach A.L., Largent B.L., Snyder S.H.: Phencyclidine and sigma opiate receptors in brain: biochemical and authoradiographical differentiation. Eur. J. Pharmacol., 1985, 113, 465–466.
24. Hellewell S.B., Bruce A., Feinstein G., Orringer J., Williams W., Bowen W.D.: Rat liver and kidney contain high densities of σ$_1$ and σ$_2$ receptors: characterization by ligand binding and photoaffinity labeling. Eur. J. Pharmacol., 1994, 268, 9–18.
25. Huber M.T., Gotthardt U., Schreiber W., Krieg J.C.: Efficacy of the sigma receptor ligand EMD 57445 (panamesine) in patients with schizophrenia: an open clinical trial. Pharmacopsychiatry, 1999, 32, 68–72.
26. Itzhak Y.: Multiple affinity binding states of the σ receptor: effect of GTP-binding protein-modifying agents. Mol. Pharmacol., 1989, 36, 512–517.
27. Itzhak Y., Kassim C.O.: Clorgyline displays high affinity for σ sites in C57-BL/6 mouse brain. Eur. J. Pharmacol., 1990, 176, 107–108.
28. Ivory J.D.: The effects of putative antipsychotic drugs and antidepressants on σ-receptors in the rat brain. M.Sc. Thesis, National University of Ireland, 1994.
29. Jordan S., Koprivica V., Altar C.A.: The antidepressant drug candidate OPC-14 523 is a partial agonist at rat and recombinant human 5-HT$_{1A}$ receptors. Soc. Neurosci. Abstr., 2000, 26, 1043.
30. Kobayashi T., Matsuno K., Murai M., Mita S.: σ$_1$ Receptor subtype is involved in the facilitation of cortical dopaminergic transmission in the rat brain. Neurochem. Res., 1997, 22, 1105–1109.
31. Koe B.K., Weissman A., Welch W.M., Browne R.G.: Sertraline, 1S,4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine, a new uptake inhibitor with selectivity for serotonin. J. Pharmacol. Exp. Ther., 1983, 226, 686–700.
32. Kornhuber J., Schoppmeyer K., Riderer P.: Affinity of 1-aminoadamantanes for the sigma binding site in postmortem human frontal cortex. Neurosci. Lett., 1993, 163, 129–131.

33. Largent B.L., Wikstrom H., Gundlach A.L., Snyder S.H.: Structural determinants of σ-receptor affinity. Mol. Pharmacol., 1987, 32, 772–784.
34. Leitner M.L., Hohmann A.G., Patrick S.L., Walker J.M.: Regional variation in the ratio of σ_1 to σ_2 binding in rat brain. Eur. J. Pharmacol., 1994, 259, 65–69.
35. Leonard B.E.: The potential contribution of sigma receptors to antidepressant actions. In: Antidepressants: New Pharmacological Strategies. Ed. Skolnick P., Humana Press, Totowa, 1997, 159–172.
36. Leonard B.E., Nicholson C.D.: σ-Ligands as potential psychotropic drugs. J. Psychopharmacol., 1994, 8, 64–65.
37. Maj J.: Repeated treatment with antidepressant drugs: responses mediated by brain dopamine receptors. In: New Results in Depression Research. Eds. Hippius H., Klerman G.L., Matussek N., Springer-Verlag, Berlin, Heidelberg, 1986, 90–98.
38. Maj J.: Pharmacology of antidepressant drugs. In: Neuropharmacology – Today and Tomorrow (Polish). Eds.: Bijak M., Lasoń W., Platan, Kraków, 2000, 71–100.
39. Maj J., Dziedzicka-Wasylewska M., Rogoż R., Rogóż Z.: Effects of antidepressant drugs administered repeatedly on the dopamine D_3 receptors in the rat brain. Eur. J. Pharmacol., 1998, 351, 31–37.
40. Maj J., Dziedzicka-Wasylewska M., Rogoż R., Rogóż Z., Skuza G.: Antidepressant drugs given repeatedly change the binding of the dopamine D_2 receptor agonist, [^{3}H]N-0437, to dopamine D_2 receptors in the rat brain. Eur. J. Pharmacol., 1996, 304, 49–54.
41. Maj J., Mogilnicka E., Klimek V., Kordecka-Magiera A.: Chronic treatment with antidepressant: potentiation of clonidine-induced aggressiveness in mice via noradrenergic mechanism. J. Neural Transm., 1981, 52, 189–197.
42. Maj J., Przegaliński E., Mogilnicka E.: Hypotheses concerning the mechanism of action of antidepressant drugs. Rev. Physiol. Biochem. Pharmacol., 1984, 100, 1–74.
43. Maj J., Rogóż Z., Skuza G., Kołodziejczyk K.: Antidepressant effects of pramipexole, a novel dopamine receptor agonist. J. Neural Transm., 1997, 104, 525–533.
44. Maj J., Rogóż Z., Skuza G., Sowińska H.: The effects of repeated treatment with antidepressant drugs on the action of D-amphetamine and apomorphine in rats. In: Neuropharmacology 85'. Eds. Keleman K., Magyar K., Vizi E.S., Académiai Kiadó, Budapest, 1985, 133–139.
45. Maj J., Rogóż Z., Skuza G., Sowińska H.: Antidepressant drugs given repeatedly increase the behavioural effects of dopamine D_2 agonist. J. Neural Transm.-Gen. Sect., 1989, 78, 1–8.
46. Maj J., Rogóż Z., Skuza G., Sowińska H.: Effects of MK-801 and antidepressant drugs in the forced swimming test in rats. Eur. Neuropsychopharmacol., 1992, 2, 37–41.
47. Maj J., Rogóż Z., Skuza G., Sowińska H.: The effects of CGP 37849 and CGP 39551, competitive NMDA receptor antagonists, in the forced swimming test. Pol. J. Pharmacol., 1992, 44, 337–346.
48. Manallack D.T., Beart P.M., Gundlach A.M.: Psychotomimetic σ-opiates and PCP. Trends Pharmacol. Sci., 1986, 7, 448–451.
49. Martin W.R., Eades C.G., Thompson J.A., Huppler E., Gilbert P.E.: The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther., 1976, 197, 517–532.
50. Matsuno K., Kobayashi T., Tanaka M.K., Mita S.: σ_1 Receptor subtype is involved in the relief of behavioral despair in the mouse forced swimming test. Eur. J. Pharmacol., 1996, 312, 267–271.
51. Matsuno K., Nakazawa N., Okamoto K., Kawashima Y., Mita S.: Binding properties of SA4503, a novel and selective σ_1 receptor agonist. Eur. J. Pharmacol., 1996, 306, 271–279.
52. Maurice T., Hiramatsu M., Itoh J., Kameyama T., Hasegawa T., Nabeshima T.: Behavioral evidence for a modulating role of σ ligands in memory processes. I. Attenuation of dizocilpine (MK-801)-induced amnesia. Brain Res., 1994, 647, 44–56.
53. Maurice T., Phan V.L., Urani A., Kamei H., Noda Y., Nabeshima T.: Neuroactive neurosteroids as endogenous effectors for the sigma$_1$ (σ_1) receptor: pharmacological evidence and therapeutic opportunities. Jpn. J. Pharmacol., 1999, 81, 125–155.
54. Maurice T., Privat A.: SA4503, a novel cognitive enhancer with σ_1 receptor agonist properties, facilitates NMDA receptor-dependent learning in mice. Eur. J. Pharmacol., 1997, 328, 9–18.
55. McCann D.J., Su T.-P.: Haloperidol-sensitive (+)-[^{3}H]SKF-10,047 binding sites (σ sites) exhibit an unique distribution in rat brain subcellular fractions. Eur. J. Pharmacol., 1990, 188, 211–218.
56. McCann D.J., Weissman A.D., Su T.-P.: Sigma-1 and sigma-2 sites in rat brain: comparison of regional, ontogenetic, and subcellular patterns. Synapse, 1994, 17, 182–189.
57. Minabe Y., Matsuno K., Ashby C.R. Jr.: Acute and chronic administration of the selective sigma$_1$ receptor agonist SA4503 significantly alters the activity of midbrain dopamine neurons in rats: in vivo electrophysiological studies. Synapse, 1999, 33, 129–140.
58. Moebius F.F., Burrows G.G., Hanner M., Schmid E., Striessing J., Glossmann H.: Identification of a 27-kDa high affinity phenylalkylamine-binding polypeptide as the σ_1-binding site by photoaffinity labeling and ligand-directed antibodies. Mol. Pharmacol., 1993, 44, 966–971.
59. Monnet F.P. Debonnel G., Junien J.-L., de Montigny C.: N-methyl-D-aspartate-induced neuronal activation is selectively modulated by σ receptors. Eur. J. Pharmacol., 1990, 179, 441–445.
60. Morin-Surun M.P., Collin T., Denavit-Saubié M., Baulieu E.E., Monnet F.P.: Intracellular σ_1 receptor modulates phospholipase C and protein kinase C ac-

tivities in the brainstem. Proc. Nat. Acad. Sci. USA, 1999, 96, 8196–8199.
61. Okuyama S., Imagawa Y., Ogawa S., Araki H., Ajima A., Tanaka M., Muramatsu M., Nakazato A., Yamaguchi K., Yoshida M.: NE-100, a novel sigma receptor ligand: in vivo tests. Life Sci., 1993, 43, PL285–290.
62. Papp M., Moryl E.: Similar effects of chronic treatment with imipramine and the NMDA antagonists CGP 37849 and MK-801 in a chronic mild stress model of depression. Eur. Neuropsychopharmacol., 1993, 3, 348–349.
63. Papp M., Moryl E.: Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur. J. Pharmacol., 1996, 263, 1–7.
64. Paul I.A., Nowak G., Layer R.T., Popik P., Skolnick P.: Adaptation of the N-methyl-D-aspartate receptor complex following chronic antidepressant treatments. J. Pharmacol. Exp. Ther., 1994, 269, 95–102.
65. Quirion R., Bowen W.D., Itzhak Y., Junien J.M., Musacchio J.M., Rothman T.P., Su T.P., Tam S.W., Taylor D.P.: A proposal on the classification of sigma binding sites. Trends Pharmacol. Sci., 1992, 13, 85–86.
66. Quirion R., Chicheportiche R., Contreras P.C., Johnson K.M., Lodge D., Tam S.W., Woods J.H., Zukin S.R.: Classification and nomenclature of phencyclidine and sigma receptor sites. Trends Pharmacol. Sci., 1987, 10, 444–446.
67. Randrup A., Munkvad I., Fog R., Gerlach J., Molander R., Kjellenberg B., Scheel-Krüger J.: Mania, depression and brain dopamine. Curr. Dev. Psychopharmacol., 1975, 2, 207–229.
68. Rao T.S., Mick S.J., Cler J.A., Emmet M.R., Dilworth V.M., Contreras P.C., Gray N.M., Wood P.L., Iyengar S.: Effects of sigma ligands on mouse cerebellar cyclic guanosine monophosphate (cGMP) levels in vivo: further evidence for a functional modulation of N-methyl-D-aspartate (NMDA) receptor complex-mediated events by sigma ligands. Brain Res., 1991, 561, 43–50.
69. Rogoż R., Dziedzicka-Wasylewska M.: Effects of antidepressant drugs on the dopamine D_2/D_3 receptors in the rat brain differentiated by agonist and antagonist binding – an authoradiographic analysis. Naunyn-Schmied. Arch. Pharmacol., 1999, 359, 178–186.
70. Rogóż Z., Skuza G., Maj J., Danysz W.: Synergistic effects of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. Neuropharmacology, 2002, 42, 1024–1030.
71. Sánchez C., Arnt J., Costall B., Kelly M.E., Meier E., Naylor R.J., Perregaard J.: The selective σ_2 ligand Lu 28-179 has potent anxiolytic-like effects in rodents. J. Pharmacol. Exp. Ther., 1997, 283, 1323–1332.
72. Sánchez C., Meier E.: Behavioural profile of SSRIs in animal models of depression, anxiety and aggression. Are they all alike? Psychopharmacology, 1997, 129, 197–205.
73. Sánchez C., Papp M.: The selective σ_2 ligand Lu 28-179 has an antidepressant-like profile in the rat chronic mild stress model of depression. Behav. Pharmacol., 2000, 11, 117–124.
74. Sánchez-Arroyos R., Guitart X.: Electrophysiological effects of E-5842, a $sigma_1$ receptor ligand and potential atypical antipsychotic, on A9 and A10 dopamine neurons. Eur. J. Pharmacol., 1999, 378, 31–37.
75. Schildkraut J.J.: The catecholamine hypothesis of affective disorders: a review of supporting evidence. Amer. J. Psychiat., 1965, 122, 509–522.
76. Senda T., Matsuno K., Okamoto K., Kobayashi T., Nakata K., Mita S.: Ameliorating effects of SA4503, a novel σ_1 receptor agonist, on memory impairments induced by cholinergic dysfunction in rats. Eur. J. Pharmacol., 1996, 315, 1–10.
77. Seth P., Fei Y.J., Li H.W., Huang W., Leibach F.H., Ganapathy V.: Cloning and functional characterization of a sigma receptor from rat brain. J. Neurochem., 1998, 70, 22–31.
78. Shirayama Y., Nishikawa T., Umino A., Takahasi K.: p-Chlorophenylalanine-reversible reduction of sigma binding sites by chronic imipramine treatment in rat brain. Eur. J. Pharmacol., 1993, 237, 117–126.
79. Skolnick P.: Antidepressants for the new millennium. Eur. J. Pharmacol., 1999, 375, 31–40.
80. Skolnick P., Layer R.T., Popik P., Nowak G., Paul I.A., Trullas R.: Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. Pharmacopsychiatry, 1996, 29, 23–26.
81. Skuza G., Góralska M., Dziedzicka-Wasylewska M.: Effects of repeated administration of SA4503, a selective receptor agonist, on dopamine receptors in rat brain. Eur. Neuropsychopharmacol., 2001, 11, Suppl. 2, S44.
82. Skuza G., Kolasiewicz W.: Repeated treatment with SA4503, a selective $sigma_1$ receptor agonist, up-regulates α_1-adrenergic system. A behavioral study. Pol. J. Pharmacol., 2001, 53, 547–550.
83. Skuza G., Rogóż Z.: Effect of 1,3-di-o-tolylguanidine (DTG), rimcazole and EMD 57445, the σ receptor ligands, in the forced swimming test. Pol. J. Pharmacol., 1997, 49, 329–335.
84. Skuza G., Rogóż Z.: A potential antidepressant activity of SA4503, a selective σ_1 receptor agonist. Behav. Pharmacol., 2002, 13, 537–543.
85. Skuza G., Rogóż Z.: Effect of combined treatment with selective σ ligands and amantadine in the forced swimming test in rats. Pol. J. Pharmacol., 2002, 54, 699–702.
86. Søby K.K., Meier E., Mikkelsen J.D.: Autoradiographic distribution of $sigma_2$ binding sites in the rat brain identified with a new receptor ligand [^{3}H]Lu 28-179. Neurosci. Abstr., 1997, 2, 1496.
87. Sulser F., Vetulani J., Mobley P.L.: Mode of action of antidepressant drugs. Biochem. Pharmacol., 1978, 27, 257–261.
88. Tottori K., Miwa T., Uwahodo Y., Yamada S., Nakai M., Oshiro Y., Kikuchi T., Altar C.A.: Antidepressant-like responses to the combined sigma and 5-HT_{1A} re-

ceptor agonist OPC-14523. Neuropharmacology, 2001, 41, 976–988.
89. Trullas R., Skolnick P.: Functional antagonists of the NMDA receptor complex exhibit antidepressant action. Eur. J. Pharmacol., 1990, 185, 1–10.
90. Ukai M., Maeda H., Nanya Y., Kameyama T., Matsuno K.: Beneficial effects of acute and repeated administrations of σ receptor agonists on behavioral despair in mice exposed to tail suspension. Pharmacol. Biochem. Behav., 1998, 61, 247–253.
91. Urani A., Roman F.J., Phan V.L., Su T.P., Maurice T.: The antidepressant-like effect induced by σ_1 receptor agonists and neuroactive steroids in mice submitted to the forced swimming test. J. Pharmacol. Exp. Ther., 2001, 298, 1269–1279.
92. Vetulani J., Nalepa I.: Antidepressants: past, present and future. Eur. J. Pharmacol., 2000, 405, 351–363.
93. Vetulani J., Sulser F.: Action of various antidepressant treatment reduces reactivity of noradrenergic cyclic AMP generating system in limbic forebrain. Nature, 1975, 257, 495–496.
94. Walker J.M., Bowen W.D., Walker F.O., Matsumoto R.R., De Costa B., Rice K.C.: Sigma receptors: biology and function. Pharmacol. Rev., 1990, 42, 355–402.
95. Willner P.: The mesolimbic dopamine system as a target for rapid antidepressant action. Int. Clin. Psychopharmacol., 1997, 12, Suppl. 3, S7–S14.
96. Wood P.L.: Pharmacology of the second messenger, cyclic guanosine 3',5'-monophosphate, in the cerebellum. Pharmacol. Rev., 1991, 43, 1–25.
97. Yamamoto H., Yamamoto Y., Sagi N., Klenerova V., Goji K.: σ Ligands indirectly modulate the NMDA receptor ion channels complex on intact neuronal cells via σ-1 sites. J. Neurosci., 1995, 15, 731–736.
98. Zou L.-B., Yamada K., Nabeshima T.: σ Receptor ligands (+)-SKF10,047 and SA4503 improve dizocilpine-induced spatial memory deficits in rats. Eur. J. Pharmacol., 1998, 355, 1–10.

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