The cholinergic system, sigma-1 receptors and cognition

van Waarde, Aren; Ramakrishnan, Nisha K.; Rybczynska, Anna; Elsinga, Philip H.; Ishiwata, Kiichi; Nijholt, Ingrid; Luiten, Paul G. M.; Dierckx, Rudi

Published in:
Behavioral Brain Research

DOI:
10.1016/j.bbr.2009.12.043

IMPORTANT NOTE: You are advised to consult the publisher’s version (publisher’s PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2011

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Review

The cholinergic system, sigma-1 receptors and cognition

Aren van Waarde\textsuperscript{a,}\textsuperscript{*}, Nisha K. Ramakrishnan\textsuperscript{a}, Anna A. Rybczynska\textsuperscript{a}, Philip H. Elsinga\textsuperscript{a}, Kiichi Ishiwata\textsuperscript{b}, Ingrid M. Nijholt\textsuperscript{c}, Paul G.M. Luitend, Rudi A. Dierckx\textsuperscript{a,}\textsuperscript{e}

\begin{itemize}
  \item \textsuperscript{a} Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 EZ Groningen, The Netherlands
  \item \textsuperscript{b} Positron Medical Center, Tokyo Metropolitan Institute of Gerontology, 1-1 Naka-cho, Itabashi-ku, Tokyo 173-0022, Japan
  \item \textsuperscript{c} Department of Neurosciences, Section Functional Anatomy, University Medical Center Groningen, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands
  \item \textsuperscript{d} Department of Molecular Neurobiology, University of Groningen, Kerklaan 30, 9751 NN Haren, The Netherlands
  \item \textsuperscript{e} Department of Nuclear Medicine, University Hospital Gent, De Pintelaan 185, 9000 Gent, Belgium
\end{itemize}

\textsuperscript{*} Corresponding author. Tel.: +31 50 3613215; fax: +31 50 3611687. E-mail address: a.van.waarde@ngmb.umcg.nl (A. van Waarde).

\begin{abstract}
This article provides an overview of present knowledge regarding the relationship between the cholinergic system and sigma-1 receptors, and discusses potential applications of sigma-1 receptor agonists in the treatment of memory deficits and cognitive disorders. Sigma-1 receptors, initially considered as a subtype of the opioid family, are unique ligand-regulated molecular chaperones in the endoplasmatic reticulum playing a modulatory role in intracellular calcium signaling and in the activity of several neurotransmitter systems, particularly the cholinergic and glutamatergic pathways. Several central nervous system (CNS) drugs show high to moderate affinities for sigma-1 receptors, including acetylcholinesterase inhibitors (donepezil), antipsychotics (haloperidol, rimcazole), selective serotonin reuptake inhibitors (fluvoxamine, sertraline) and monoamine oxidase inhibitors (clorglycine). These compounds can influence cognitive functions both via their primary targets and by activating sigma-1 receptors in the CNS. Sigma-1 agonists show powerful anti-amnesic and neuroprotective effects in a large variety of animal models of cognitive dysfunction involving, among others (i) pharmacologic target blockade (with muscarinic or NMDA receptor antagonists or \textit{p}-chloroamphetamine); (ii) selective lesioning of cholinergic neurons; (iii) CNS administration of \textit{\beta}-amyloid peptides; (iv) aging-induced memory loss, both in normal and senescent-accelerated rodents; (v) neurodegeneration induced by toxic compounds (CO, trimethyltin, cocaine), and (vi) prenatal restraint stress.
\end{abstract}

\textsuperscript{©} 2010 Elsevier B.V. All rights reserved.

1. Introduction ................................................................. 544
2. Acetylcholine and sigma-1 receptor function ................................................................. 544
3. Changes of sigma receptor density in aging and neurodegenerative disease ................................................................. 545
4. Sigma ligands improve cognition in animal models of cognitive impairment ................................................................. 546
5. Improvement of cognitive function in humans ................................................................. 548
6. Modulation of glutamate release by sigma-1 agonists ................................................................. 549
7. Modulation of the NMDA response by sigma-1 agonists ................................................................. 549
8. Modulation of calcium homeostasis ................................................................. 550
9. Involvement of sigma-1 receptors in neuronal differentiation and neuroplasticity ................................................................. 550
10. Conclusion ................................................................. 551

References ........................................................................ 551

1. Introduction

Cholinergic neurotransmission is a crucial process underlying memory and cognitive function. Cholinergic basal forebrain neurons in the nucleus basalis magnocellularis innervate the cerebral cortex, amygdaloid complex, or hippocampus and are essential for learning and memory formation [1,28]. Some cortical cholinergic activity is lost in normal aging. Patients suffering from AD or related dementias display a severe degeneration of cholinergic neurons and a corresponding loss of cortical cholinergic neurotransmission, which is one of the factors underlying their memory deficits [4,18,19]. Administration of an anticholinergic drug, such as the muscarinic antagonist scopolamine, to experimental animals or healthy volunteers results in striking impairments of memory function which resemble Alzheimer dementia [131]. On the other hand, acetylcholinesterase (AChE) inhibitors such as tacrine, physostigmine, rivastigmine and galantamine which suppress breakdown of the neurotransmitter acetylcholine, can temporarily improve memory function in some demented patients and in animal models of amnesia [64].

The sigma-1 receptor, a unique orphan receptor, is strongly expressed in neurons and in glia [35,37]. Neurosteroids, i.e. steroid hormones which are synthesized within the brain itself [84,95,101,143], and sphingolipids [134] interact with sigma-1 sites which are now considered as ligand-regulated molecular chaperones modulating the activity of voltage-regulated ano, and ligand-gated ion channels [98], intracellular calcium signaling [39], and the release of various neurotransmitters including acetylcholine [45,58,63] and glutamate [107]. Occupancy of sigma-1 receptors by agonists causes translocation of the receptor protein from the endoplasmatic reticulum to the cell membrane where the receptor can regulate ion channels and neurotransmitter release [36,39] (Fig. 1). The sigma-1 receptor is implicated in cellular differentiation [37,40], neuroplasticity [145,149], neuroprotection [71,89], and cognitive functioning of the brain [85].

As both the cholinergic system and sigma-1 receptors are implied in cognition, we will in this article present an overview of current knowledge regarding the relationship between these neuronal pathways, and discuss potential applications of sigma-1 receptor agonists in the treatment of memory deficits and cognitive disorders.

2. Acetylcholine and sigma-1 receptor function

Sigma-1 receptor agonists are potent modulators of acetylcholine release, both in vitro and in vivo. Igmesine and (+)-SKF 10,047 potentiate the KCl-evoked release of 3H-acetylcholine from rat hippocampal slices, and this effect can be blocked by the sigma antagonist haloperidol [58]. The sigma-1 receptor agonist SA4503 dose-dependently increases the electrically evoked release of 3H-acetylcholine from hippocampal but not striatal slices isolated from rat brain [45].

In using in vivo microdialysis in freely moving rats, extracellular acetylcholine levels in the frontal cortex were found to be acutely and dose-dependently increased upon administration of the sigma-1 receptor agonists (+)-SKF 10,047, (+)-3-PPP, (±)-pentazocine and DTG. The effect of SKF 10,047 was stereoselective and it could be reversed by the sigma antagonist haloperidol [75,76]. In later experiments, (+)-SKF 10,047 was shown to also increase extracellular acetylcholine in the hippocampus in a stereoselective fashion and this effect could also be blocked by haloperidol [77]. Regional differences in the stimulation of acetylcholine release by sigma-1 receptor agonists were subsequently observed. (+)-SKF 10,047 and DTG increased the release of acetylcholine in hippocampus and frontal cortex, but in the rat striatum, DTG had no and (+)-SKF 10,047 had only a marginal effect [62]. Acetylcholine release in the hippocampus and frontal cortex was also strongly increased by the sigma-1 agonist SA4503, whereas acetylcholine release in the striatum was not affected [63,79] (see Fig. 2). The absence of an increase of striatal acetylcholine levels after administration of sigma-1 receptor agonists may be the reason why such drugs do not display some undesired side effects which are frequently seen after administration of acetylcholinesterase (AChE) inhibitors [63].

Since selective sigma-1 receptor agonists can facilitate the activity of cholinergic systems by stimulating acetylcholine release, particularly in the cortex and hippocampus, such drugs have the potential to ameliorate the memory impairments resulting from cholinergic dysfunction.

However, the capability of sigma-1 receptor agonists to ameliorate such impairments appears to be not solely due to modulation of residual acetylcholine release. In a recent study involving the potent and selective sigma-1 agonist (±)-PPCC (Ki at muscarinic receptors >10,000 nM) and cholinergic lesions of varying severity, it was noted that the anti-amnesic effects of the sigma receptor ago-
Fig. 2. Upper panel: The sigma-1 receptor agonist SA4503 (10 mg/kg, per os, administered at time zero) increases extracellular acetylcholine levels in the frontal cortex but not in the striatum of freely moving rats. Lower panel: The effect of SA4503 on acetylcholine release is counteracted by the sigma-1 receptor antagonist NE-100 (0.5 mg/kg, co-administered with SA4503). After [63,79].

Fig. 3. Age-related increases of sigma-1 receptor density in rhesus monkey brain (upper left) compared to the decreases of muscarinic M1/M4, serotonin-2A (5-HT2A), and dopamine D2/D3 receptor numbers with aging in human brain. Data from [60], [122], [142], and [46], respectively.
sigma-1 receptor allele, genotype, haplotype, and diplotype distributions were observed between the studied groups [73].

In a small group of patients with early Parkinson’s disease (n = 6), the BP of 11C-SA4503 was found to be significantly lower on the more affected than the less affected side of the anterior putamen, although there was no significant difference in BP between patients and controls [108]. These data suggest that Parkinson’s disease may be associated with a loss of sigma-1 receptors from the putamen, although the decrease is less striking than that observed in the cerebral cortex in AD.

In the rodent brain, sigma-1 receptor density was generally found to be preserved during aging. In a recent study involving healthy controls and senescent-accelerated mice (SAM), no differences between 6-, 9- and 12-month-old rodents regarding the sigma-1 receptor density of various brain regions were observed, neither at the level of mRNA nor at the protein level [histochemistry, binding of 3H- (+)-SKF 10,047]. However, in aged (12-month) SAM, the antidepressant efficacy of the sigma-1 agonist igmesine was increased. This augmented response may be due to decreased levels of neurosteroids in these animals, particularly progesterone, a steroid with sigma-1 receptor antagonist action [132]. The efficacy of sigma-1 receptor agonists is known to be inversely correlated to brain progesterone levels. In rats treated with chronic intracerebroventricular infusion of β-amyloid(1–40) protein, or in β-amyloid(25–35) peptide-treated mice, a significant decrease of cerebral progesterone levels is accompanied by a corresponding increase of the antidepressant activity of sigma-1 receptor agonists [154, 155]. In another study on murine aging, no differences in cerebral sigma-1 receptor density were observed between 2- and 24-month-old C57/BL6 mice, neither at the mRNA nor at the protein level [133].

Changes of sigma-1 and sigma-2 receptors in aging rat brain have been examined as well, by applying the radioligands 3H-SA4503, 3H- (+)-pentazocine and 3H-DTG for binding studies in brain homogenates of 1.5-, 6-, 12- and 24-month-old Fisher-344 rats. The number of binding sites increased with aging, but the binding affinity of all ligands was decreased. Apparently, increases of receptor density (over)compensate for a reduced affinity of the receptor proteins to agonists in this rodent strain, and as a consequence, ligand binding is increased at old age [51], particularly at ages greater than 12 months. In an older study which used 3H-haloperidol (in combination with 50 nM unlabeled spiperone) to quantify sigma-1 plus sigma-2 receptors, receptor density in the brain of Fisher-344 rats was found to be unaltered between postnatal day 1 and age 12 months [69].

These findings of a preserved receptor density may perhaps not be generalized to all rat strains, since middle-aged Sprague–Dawley rats (5–6 months old) were reported to have fewer sigma binding sites and sites with lower affinity for 3H-DTG than young adult animals (2–3 months old). The older animals also exhibited a decreased behavioral response to sigma ligands injected into the substantia nigra [74]. Another research group which used 3H-(+)-PPP confirmed that the binding sites for this ligand in the brain of Sprague–Dawley rats are present at high density during the perinatal period, and decline thereafter [129].

4. Sigma ligands improve cognition in animal models of cognitive impairment

Sigma-1 agonists (applied systemically) have shown antiamnesic efficacy in several animal models of cognitive impairment. Both pharmacological and pathological models of amnesia have been examined (see Table 1 for an overview). These include: (i) cholinergic deficits (either induced by muscarinic antagonists or by lesions of the forebrain or the nucleus basalis resulting in a selective loss of cholinergic neurons); (ii) pathology induced by direct administration of β-amyloid(25–35) peptide to the rodent CNS, an animal model of Alzheimer’s disease; (iii) aging-induced losses of memory function, both in normal mice and SAM; (iv) neurodegeneration caused by exposure of animals to CO gas, or to trimethyltin; (v) prenatal stress (restraint, or exposure to cocaine), and (vi) glutamatergic, serotonergic, or calcium channel deficits induced by various drugs. The beneficial effects of sigma-1 receptor agonists on cognitive performance were detected in many different cognitive tests assessing short-term (working memory), long-term (reference memory), contextual or spatial memory processes.

For example, the sigma-1 receptor agonists (+)-SKF 10,047, pentazocine, DTG, (+)-3-PPP, igmesine and SA4503 prevented the scopolamine-induced amnesia of mice and rats in passive avoidance tasks, and the beneficial action of these compounds was blocked by sigma-1 receptor antagonists like NE-100. The anti-amnesic effects of SA4503 were blocked after sigma-1 receptor antisense administration, but not after administration of a mismatch oligodeoxynucleotide [79, 80, 81, 93, 139]. Thus, activation of the sigma-1 receptor is involved in the improvement of cognition, and sigma-1 agonists have potential for the treatment of amnesia resulting from cholinergic dysfunction.

Sigma-1 receptor agonists such as (+)-SKF 10,047, (+)-pentazocine, DTG, PRE084 and SA4503 also showed a potent anti-amnesic action against the cognitive deficits induced by NMDA-receptor blockade in mice and rats, e.g. treatment of animals with the non-competitive NMDA receptor antagonist dizocilpine before the learning test. These beneficial effects were stereoselective and were blocked by pretreatment of animals with sigma-1 antagonists such as BMY14802, haloperidol or NE-100 (see Table 1 for references).

Neurotoxicity models of cognitive impairment which have been employed for testing cognitive enhancement by sigma-1 receptor agonists include repeated exposure of mice to CO gas and trimethyltin administration to rats. The former model results after 5–7 days in neuronal death that remains restricted to the CA1 area of the hippocampus [118]. Trimethyltin administration results in damage of selective neural populations from limbic structures of the brain [10, 11]. In such neurotoxicity models, similar findings were obtained as in the pharmacological models of amnesia, i.e. sigma-1 receptor agonists improved cognitive performance and this improvement could be blocked by sigma-1 receptor antagonists. However, in contrast to the scopolamine or dizocilpine-induced amnesia, cognitive impairments after exposure of animals to CO or trimethyltin were alleviated not only by sigma-1 agonists but also by sigma-2 receptor antagonists.

In most behavioral tests, sigma-1 receptor agonists do not facilitate and sigma-1 receptor antagonists do not impede the learning of healthy control animals. Downregulation of sigma-1 receptor expression using an in vivo antisense approach also does not affect the learning ability of healthy mice submitted to a passive avoidance test [93, 94]. However, sigma-1 receptor agonists improve the performance of pharmacologically or pathologically lesioned animals in standard learning tests, and this improvement in lesioned rodents can be blocked by sigma-1 receptor antagonists. Neuroactive steroids (such as DHEA-S or pregnenolone sulfate) have similar effects as non-steroid sigma-1 receptor agonists, whereas progesterone behaves as a sigma-1 receptor antagonist. These observations suggest that sigma-1 receptors are not directly involved in learning or memory, but sigma-1 receptor agonists can modulate neural processes underlying cognition, particularly under pathological conditions.

However, in some publications pro-mnesic effects of sigma-1 receptor agonists have been reported. For example, the neurosteroids DHEA-S and PREG-S, when given either pre- or post-training, were found to facilitate retention of a modified learning task in mice in a dose-dependent manner with a bell-
<table>
<thead>
<tr>
<th>Amnesia model</th>
<th>Species</th>
<th>(\sigma_1) agonists</th>
<th>(\sigma_1) antagonists</th>
<th>Other drugs used</th>
<th>Behavioral tests</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic deficit</td>
<td>Rat</td>
<td>Igmesine, (+)-3-PPP, DTG</td>
<td>None</td>
<td>Piracetam</td>
<td>Passive avoidance</td>
<td>[25]</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, (±)-pentazocine</td>
<td>None</td>
<td>None</td>
<td>Passive avoidance</td>
<td>[81]</td>
</tr>
<tr>
<td>Scopolamine, ibotenic acid forebrain lesion</td>
<td>Rat</td>
<td>Haloperidol, NE-100</td>
<td>None</td>
<td>None</td>
<td>Passive avoidance</td>
<td>[141]</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Mouse</td>
<td>(±)-SKF 10,047, (±)-pentazocine</td>
<td>None</td>
<td>None</td>
<td>Passive avoidance</td>
<td>[139]</td>
</tr>
<tr>
<td>Ibotenic acid forebrain lesion</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, physostigmine</td>
<td>None</td>
<td>None</td>
<td>Morris water maze, Y-maze, water maze, passive avoidance</td>
<td>[140, 152, 93]</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Rat</td>
<td>SA4503</td>
<td>None</td>
<td>None</td>
<td>Mismatch antisense</td>
<td>[148]</td>
</tr>
<tr>
<td>Nucleus basalis lesion</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, physostigmine</td>
<td>None</td>
<td>None</td>
<td>Morris water maze, Active avoidance</td>
<td>[53]</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Mouse</td>
<td>ANAVEX1-41</td>
<td>Antisense, NE-100</td>
<td>None</td>
<td>Y-maze, Passive avoidance, water maze</td>
<td>[43, 41, 42]</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Mouse</td>
<td>Dimemorfan</td>
<td>Haloperidol</td>
<td>None</td>
<td>Passive avoidance</td>
<td>[158]</td>
</tr>
<tr>
<td>192IgG-saporin induced lesions, atropine sulfate</td>
<td>Rat</td>
<td>(±)-PPCC</td>
<td>BD1047</td>
<td>None</td>
<td>Passive avoidance, water maze</td>
<td>[2]</td>
</tr>
<tr>
<td>l-NAME, 7-nitroindazole</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, (+)-pentazocine</td>
<td>None</td>
<td>None</td>
<td>Y-maze</td>
<td>[70]</td>
</tr>
<tr>
<td>Amyloid-induced neurodegeneration</td>
<td>Mouse</td>
<td>(+)-Pentazocine, PRE084, DHEA, PREG-S, DHEA-S</td>
<td>None</td>
<td>None</td>
<td>Y-maze, Passive avoidance</td>
<td>[100]</td>
</tr>
<tr>
<td>β-Amyloid(25–35) peptide</td>
<td>Mouse</td>
<td>(+)-Pentazocine, BMY14802, progestosterone</td>
<td>None</td>
<td>None</td>
<td>Y-maze, Passive avoidance</td>
<td>[105]</td>
</tr>
<tr>
<td>β-Amyloid(25–35) peptide</td>
<td>Mouse</td>
<td>BD1047</td>
<td>Tarcine, rivastigmine, galantamine</td>
<td>Y-maze, passive avoidance</td>
<td>[157]</td>
<td></td>
</tr>
<tr>
<td>β-Amyloid(25–35) peptide</td>
<td>Mouse</td>
<td>BD1047</td>
<td>Scopolamine</td>
<td>Y-maze, passive avoidance, radial arm maze, Y-maze, passive avoidance</td>
<td>[158]</td>
<td></td>
</tr>
<tr>
<td>Aging-related memory loss</td>
<td>Mouse</td>
<td>Igmesine, PRE084</td>
<td>BMY14802, JO1783</td>
<td>None</td>
<td>Y-maze, Water maze</td>
<td>[97]</td>
</tr>
<tr>
<td>Senescence-accelerated mouse</td>
<td>Mouse</td>
<td>PRE084</td>
<td>None</td>
<td>None</td>
<td>Water maze, Passive avoidance</td>
<td>[82]</td>
</tr>
<tr>
<td>Normal aging</td>
<td>Mouse</td>
<td>PRE084</td>
<td>None</td>
<td>None</td>
<td>Morris water maze</td>
<td>[148]</td>
</tr>
<tr>
<td>Normal aging</td>
<td>Mouse</td>
<td>PRE084</td>
<td>None</td>
<td>None</td>
<td>Morris water maze</td>
<td>[133]</td>
</tr>
<tr>
<td>Hypoxia-induced neurodegeneration</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, DTG</td>
<td>BMY14802</td>
<td>None</td>
<td>Y-maze, Passive avoidance</td>
<td>[87]</td>
</tr>
<tr>
<td>Repeated CO exposure</td>
<td>Mouse</td>
<td>PRE084, DTG, BD1008</td>
<td>NE-100</td>
<td>None</td>
<td>Passive avoidance</td>
<td>[92]</td>
</tr>
<tr>
<td>Repeated CO exposure</td>
<td>Mouse</td>
<td>DHEA</td>
<td>None</td>
<td>None</td>
<td>Y-maze, Passive avoidance</td>
<td>[91]</td>
</tr>
<tr>
<td>Repeated CO exposure</td>
<td>Mouse</td>
<td>Donepezil, Igmesine</td>
<td>BD1047</td>
<td>Tarcine, rivastigmine, galantamine</td>
<td>Y-maze, passive avoidance</td>
<td>[104]</td>
</tr>
<tr>
<td>Toxic-induced neurodegeneration (aspecific)</td>
<td>Mouse</td>
<td>PRE084, DTG, BD1008</td>
<td>NE-100, haloperidol</td>
<td>None</td>
<td>T-maze, water maze, passive avoidance</td>
<td>[103]</td>
</tr>
<tr>
<td>Trimethyltin</td>
<td>Rat</td>
<td>Igmesine</td>
<td>None</td>
<td>None</td>
<td>Passive avoidance</td>
<td>[124]</td>
</tr>
<tr>
<td>Trimethyltin</td>
<td>Mouse</td>
<td>PRE084, DTG, BD1008</td>
<td>None</td>
<td>None</td>
<td>Passive avoidance</td>
<td>[92]</td>
</tr>
<tr>
<td>Prenatal stress</td>
<td>Rat</td>
<td>Igmesine</td>
<td>BD1063</td>
<td>None</td>
<td>Y-maze, T-maze, water maze, passive avoidance</td>
<td>[106]</td>
</tr>
<tr>
<td>Prenatal cocaine exposure</td>
<td>Rat</td>
<td>Igmesine, DHEA</td>
<td>BD1063</td>
<td>None</td>
<td>T-maze, Water maze, Passive avoidance</td>
<td>[106]</td>
</tr>
<tr>
<td>NMDA-receptor deficit</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, (+)-pentazocine</td>
<td>BMY14802, NE-100</td>
<td>(−)-SKF 10,047, (−)-pentazocine</td>
<td>Y-maze, Passive avoidance, elevated plus maze</td>
<td>[86]</td>
</tr>
<tr>
<td>Dizocilpine</td>
<td>Mouse</td>
<td>DHEA-S</td>
<td>BMY14802, haloperidol</td>
<td>None</td>
<td>Y-maze, Passive avoidance</td>
<td>[126]</td>
</tr>
<tr>
<td>Dizocilpine</td>
<td>Mouse</td>
<td>SA4503</td>
<td>Haloperidol, progestosterone</td>
<td>l-NAME</td>
<td>Y-maze, Passive avoidance</td>
<td>[96]</td>
</tr>
</tbody>
</table>
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Amnesia model</th>
<th>Species</th>
<th>$\sigma_1$ agonists</th>
<th>$\sigma_1$ antagonists</th>
<th>Other drugs used</th>
<th>Behavioral tests</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizocilpine</td>
<td>Rat</td>
<td>(+)-SKF 10,047, SA4503, DHEA-S, PREG-S</td>
<td>NE-100</td>
<td>None</td>
<td>Radial arm maze</td>
<td>[163]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Radial arm maze</td>
<td>[162]</td>
</tr>
<tr>
<td>Dizocilpine</td>
<td>Mouse</td>
<td>PRE084, DHEA-S, SAV503</td>
<td>Antisense</td>
<td>Mismatch antisense</td>
<td>Y-maze, passive avoidance</td>
<td>[93]</td>
</tr>
<tr>
<td>Dizocilpine</td>
<td>Mouse</td>
<td>PRE084, DHEA-S, SAV503</td>
<td>Antisense</td>
<td>Mismatch antisense</td>
<td>Y-maze, passive avoidance</td>
<td>[94]</td>
</tr>
<tr>
<td>Phenycyclidine, dizocilpine</td>
<td>Mouse</td>
<td>PRE084, DHEA-S, (+)-pentazocine, (+)-SKF 10,047</td>
<td>NE-100</td>
<td>D-cycloserine, t-NAME</td>
<td>One-trial water-finding task</td>
<td>[121]</td>
</tr>
<tr>
<td>Phenycyclidine</td>
<td>Mouse</td>
<td>Donepezil, igmesine</td>
<td>Antisense, BD1047</td>
<td>Rivastigmine, tacrine</td>
<td>Y-maze, passive avoidance</td>
<td>[90]</td>
</tr>
<tr>
<td>Phenycyclidine</td>
<td>Mouse</td>
<td>Fluvoxamine, SA4503, DHEA-S</td>
<td>NE-100</td>
<td>Paroxetine</td>
<td>Novel object recognition task</td>
<td>[31]</td>
</tr>
<tr>
<td>Phenycyclidine</td>
<td>Mouse</td>
<td>Donepezil</td>
<td>NE-100</td>
<td>Physostigmine</td>
<td>Novel object recognition task</td>
<td>[65]</td>
</tr>
<tr>
<td>Serotonergic deficit</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, (+)-pentazocine, DTG, (+)-3-PPP</td>
<td>None</td>
<td>Ritanserin, mianserin, tacrine, physostigmine</td>
<td>Passive avoidance</td>
<td>[81]</td>
</tr>
<tr>
<td>p-Chloroamphetamine</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, (+)-pentazocine, DTG, (+)-3-PPP</td>
<td>None</td>
<td>(-)-SKF 10,047, hemicholinium-3</td>
<td>Passive avoidance</td>
<td>[80]</td>
</tr>
<tr>
<td>Ca$^2+$ channel deficit</td>
<td>Mouse</td>
<td>PRE084</td>
<td>BMY14802</td>
<td>None</td>
<td>Y-maze, passive avoidance, water maze</td>
<td>[99]</td>
</tr>
<tr>
<td>Sigma receptor deficit</td>
<td>Mouse</td>
<td>(+)-SKF 10,047, DTG, (+)-3-PPP</td>
<td>None</td>
<td>None</td>
<td>Passive avoidance</td>
<td>[78]</td>
</tr>
</tbody>
</table>

shaped dose–response curve. This action of the neurosteroids appears to be dependent on their interaction with sigma-1 receptors, since it can be blocked by concurrent administration of the sigma antagonist haloperidol [135]. Long-term potentiation (LTP) in rat hippocampus, a process thought to be crucial for learning and memory, is facilitated after chronic (7 days) administration of the neurosteroid DHEA-S. This potentiation appears to be based on alterations in postsynaptic neurons since no changes were observed in presynaptic glutamate release. DHEA-S appears to act through sigma-1 receptors, since the potentiating effect is absent when sigma-1 receptor antagonists (NE-100, haloperidol) are co-administered with the neurosteroid [12]. Another neurosteroid with sigma-1 receptor agonist action, PREG-S, has also been reported to facilitate LTP in the rodent hippocampus by a mechanism involving sigma-1 receptors and L-type calcium channels [136]. The non-sulfated forms of the neurosteroids which lack the sigma-1 receptor agonist action (DHEA and PREG) do not potentiate LTP [12,136]. Paired-pulse facilitation in hippocampal neurons from adult rats, a short-term increase of the postsynaptic potential, is also potentiated by PREG-S and this potentiation is abolished after co-administration of sigma-1 receptor antagonists [138].

5. Improvement of cognitive function in humans

Fluvoxamine has been reported to be effective in improving cognitive impairments in an animal model of schizophrenia, in contrast to paroxetine [31]. Interestingly, fluvoxamine but not paroxetine was also found to improve the lack of concentration, poor memory, slowness of mind, and poor executive function in a patient with schizophrenia [54]. The affinity of fluvoxamine for sigma-1 receptors is more than 50 times higher than that of paroxetine, although both compounds are potent selective serotonin reuptake inhibitors (SSRIs) [119]. High occupancy (up to 60%) of sigma-1 receptors in the human brain was observed with $^{11}$C-SA4503 PET after a single oral dose of 200 mg fluvoxamine [48] (see Fig. 4 for a similar occupancy study). These data suggest that sigma-1 receptor agonists including SSRIs with sigma-1 receptor agonist action, such as fluvoxamine, may be candidates for treating cognitive impairments in schizophrenia.

Compounds which combine acetylcholinesterase (AChE) inhibition with sigma-1 receptor agonism exist as well, e.g. donepezil. A recent paper reported that therapeutic doses of donepezil result in considerable sigma-1 receptor occupancy in human brain [49].

![PET scans of the brain of a human volunteer](image-url)

Fig. 4. PET scans of the brain of a human volunteer, made with the sigma-1 receptor ligand $^{11}$C-SA4503, at baseline (left) and after oral administration of an antipsychotic drug, interval 3 h (middle) and 10 h (right), respectively. The binding of $^{11}$C-SA4503 was considerably reduced after occupancy of sigma-1 receptors by the antipsychotic drug. Data from our own group, not previously published.
Sigma-1 receptor agonists may have potential for treating AD since the compounds are not only capable of alleviating cognitive deficits in animal models of cognitive impairment (see above) but they can also provide neuroprotection against amyloid toxicity (see [83] for a review). Evidence for such neuroprotective activity has been provided both by in vitro experiments in cultured cortical neurons [71] and by in vivo studies in rodents [105,157]. Recently, it was found that sigma-1 receptor agonists can powerfully suppress microglial activation [29]. Such compounds may therefore attenuate the inflammatory component in neurodegenerative diseases.

More applications of sigma-1 receptor agonists, e.g. in the treatment of depression, anxiety, psychosis, substance abuse, stroke and neuropathic pain are discussed in several recent reviews [13,14,32,40,85,98]. Companies involved in the development of drugs for such indications include M's Science, AGY Therapeutics, Otsuka American Pharmaceutical, and Sanofi-Aventis [14].

6. Modulation of glutamate release by sigma-1 agonists

Besides the well-known deficits of acetylcholine, the neurotransmitter glutamate can be reduced in AD. Both neurotransmitters are supposed to play vital roles in memory [1]. It is thus of interest that sigma ligands are capable of modulating glutamate release in various areas of the brain.

The neurosteroid PREGs (which is supposed to act as a sigma-1 receptor agonist) and the sigma-1 receptor agonist (+)-pentazocine, but not the (-)-enantiomers of PREGs and pentazocine, or the inactive steroid isopregnanolone enhance the spontaneous release of glutamate in cultured hippocampal neurons. The sigma receptor antagonists haloperidol and BD1063 and a membrane-permeable calcium chelator block this effect of PREGs. These results suggest that hippocampal glutamate release can be enhanced via activation of presynaptic sigma-1 receptors and an elevation of the levels of intracellular Ca2+ [107]. Later studies by another research group confirmed that the spontaneous release of glutamate is enhanced by PREGs both in the hippocampus and in prelimbic cortex, but not in the striatum. The effect of PREGs in the prelimbic cortex appears to be mediated via alpha-1 adrenergic and sigma-1 receptors, whereas the effect in the hippocampus is dependent on sigma-1 receptors only. Intracellular calcium released from the endoplasmatic reticulum plays a key role in the enhancement of glutamate release [24]. DHEA-S, another neurosteroid with sigma-1 receptor agonist action, also enhances the spontaneous release of glutamate in prelimbic cortex and hippocampus. The effect of this compound in the prelimbic cortex appears to be mediated via dopamine D1 and sigma-1 receptors, whereas that in the hippocampus occurs only via sigma-1 receptors [23].

Brain-derived neurotrophic factor (BDNF)-induced glutamate release in cultured cortical neurons is potentiated by antidepressants with sigma-1 receptor agonist activity such as fluvoxamine and imipramine, and this potentiation is blocked by the sigma-1 receptor antagonist BD1047. Not only pharmacological activation but also overexpression of the sigma-1 receptor enhances BDNF-enhanced glutamate release. The sigma-1 receptor appears to play an important role in BDNF signaling leading to the release of glutamate, and the enhancement of glutamate release seems to occur via the PLC-gamma/IP3/Ca2+ pathway [180].

Thus, sigma ligands represent a strategy for modulating glutamatergic activity within the mammalian brain, and such modulation could be an additional mechanism underlying the antiamnesic action of sigma-1 receptor agonists.

7. Modulation of the NMDA response by sigma-1 agonists

NMDA receptors mediate the induction of LTP and long-term depression in various brain areas (i.e. long-lasting improvements and impairments of synaptic transmission) [3,15,30,55]. Such forms of synaptic plasticity are considered as important cellular mechanisms underlying learning and memory [9,68,147].

Pharmacological inhibition of NMDA receptor function, by administration of NMDA antagonists either directly into the brain or by systemic administration of compounds which can cross the blood–brain barrier, results in impaired spatial learning and non-spatial passive avoidance learning in rodents [16,117,130,156]. Knockout mice lacking the NMDA receptor 1 gene in CA1 pyramidal cells of the hippocampus exhibit impaired spatial learning but unimpaired nonspatial learning [150]. Apparently, NMDA-dependent strengthening of CA1 synapses is essential for the acquisition and storage of spatial memory.

In many studies, sigma-1 receptor agonists were shown to modulate responses induced by NMDA receptor activation in various brain areas such as the hippocampus and prefrontal cortex. Some responses are potentiated and others inhibited by sigma-1 receptor agonists. Sigma-1 receptor agonists when administered alone are without any effect, but these compounds block the agonist-induced modulation.

For example, the electrophysiological response of pyramidal neurons in the CA3 region of the rat dorsal hippocampus to NMDA (excitatory activation) is potentiated by sigma-1 receptor agonists such as (+)-pentazocine, DTG, BD737, igmesine, L687,384, or DHEA and therapeutic drugs with significant sigma-1 receptor agonist affinity (the SSRI sertraline and the monoamine oxidase inhibitor clorgyline), whereas this potentiation is reversed by sigma-1 receptor antagonists such as haloperidol, BMV14802, NE-100, progesterone and testosterone [5,6,8,20,112,113,114]. The potentiation persists for at least 60 min and can be sustained by prolonged microiontophoretic application of a sigma-1 receptor agonist, indicating that sigma-1 receptors do not rapidly desensitize [5].

Steroid hormones with antagonist action such as progesterone and testosterone produce a tonic dampening of the function of sigma-1 receptors and, consequently, of NMDA-mediated responses. Pregnancy reduces sigma-1 receptor function in the brain, since a tenfold higher dose of sigma-1 receptor agonists is required to potentiate the NMDA response of pyramidal neurons in pregnant female rats than in non-pregnant control animals [7].

In an electrophysiological study in which animals were unilaterally lesioned by local injection of colchicine into the mossy fiber system (an afferent system to CA3 pyramidal neurons), the potentiating effect of (+)-pentazocine on the NMDA response was found to persist on the lesioned side, but the potentiating effects of DTG and igmesine were abolished after lesioning [21]. These data were interpreted as suggesting that the test drugs were acting on two different subtypes of sigma receptors, and that the receptors for DTG and igmesine are located on the mossy fiber terminals, in contrast to the receptors for (+)-pentazocine [21]. In a later study, the effect of the sigma-2 subtype-selective ligand siramesine was tested on the neuronal response to NMDA in the CA3 region of the rat dorsal hippocampus. Siramesine was found to potentiate the NMDA response dose-dependently with a bell-shaped curve, but the effect of siramesine could – in contrast to the effect of sigma-1 receptor agonists – not be reversed by NE-100, haloperidol or progesterone [17]. Thus, not only sigma-1 but also sigma-2 receptors appear to be involved in modulation of the NMDA response.

Bell-shaped dose–response curves are a common finding in studies regarding the effect of sigma-1 receptor agonists. At low doses the NMDA response is potentiated but at higher dose the potentiation is reversed [5,8,111,112]. For example, the sigma-1 receptor agonist SR 31742A increases NMDA-induced inward currents of pyramidal cells in slices of rat medial prefrontal cortex at doses ranging from 10 nM to 100 nM (EC50 23 nM), but at doses greater than 100 nM an inhibition is observed [66]. The potentiation...
ton of NMDA-receptor-mediated neurotransmission by SR 31742A may account for the antipsychotic and cognition-enhancing properties of the drug, whereas the inhibition of NMDA responses at higher drug concentrations may account for its neuroprotective effect [66].

Recently, a molecular mechanism has been proposed which may explain how sigma-1 receptor ligands increase the NMDA response. Calcium ions entering the cells through NMDA-receptor-related channels normally activate a potassium current via small-conductance calcium-activated K⁺ channels (SK channels). This current shunts the NMDA receptor responses. Sigma-1 subtype-selective receptor agonists prevent SK channel opening, and consequently increase the NMDA receptor response [72].

8. Modulation of calcium homeostasis

The intracellular localization of sigma-1 receptors (mainly in endoplasmatic reticulum, but also in nuclear and plasma membranes and on mitochondria [52,57,102,133,137]) suggests that these binding sites could be involved in the regulation of calcium mobilization.

Indeed, sigma-1 receptor activation has been shown to affect calcium homeostasis. Sigma-1 receptor agonists increased contractility, beating rate and calcium influx in cultured cardiac myocytes from neonatal rats [26]. Intracellular levels of inositol triphosphate in these cells were increased as well [123]. In NG108 (neuroblastoma–glioma) cells, various sigma-1 receptor agonists enhanced the bradykinin-induced increases in cytosolic free calcium with bell-shaped dose–response curves whereas this effect could be blocked by a sigma-1 receptor antisense oligonucleotide, suggesting that sigma-1 receptor activation facilitates IP3-receptor-mediated Ca²⁺ signaling [34]. In SH-SY5Y (neuroblastoma) cells, the sigma-1 receptor agonist (+)-pentazocine and various neurosteroids also potentiated the bradykinin-induced Ca²⁺ response, and this potentiation was blocked by the sigma receptor antagonists haloperidol and progesterone [44]. By expression of either complete sigma-1 receptors or the N- or C-terminal segment of the sigma-1 receptor protein in MCF-7 breast cancer cells (which normally express few sigma-1 receptors), proof was obtained that sigma-1 receptor overexpression results in an enhancement of bradykinin-, vasopressin- or ATP-induced calcium release, and that the C-terminal segment of the sigma-1 receptor is involved in the interaction with the inositol triphosphate receptor–ankyrin-B 220 complex [159].

Experiments in adult guinea pig isolated brainstem preparations have indicated that sigma-1 receptor activation leads to activation of phospholipase C and the beta-1 and beta-2 isoforms of protein kinase C [116]. In isolated rat hippocampal neurons, receptor activation leads to a potentiation of NMDA-receptor-mediated increases of free intracellular calcium [115]. However, in rat frontal cortical neurons, sigma receptor ligands were found to reduce the NMDA-induced Ca²⁺ influx. Sigma-1-subtype-selective compounds (igmesine, (+)-pentazocine) particularly affected the sustained phase of the Ca²⁺ response to NMDA, whereas non-subtype-selective compounds (DTG, haloperidol) reduced the initial and sustained phases to the same degree. The inhibition of the sustained phase was directly related to the affinity of the ligands to sigma-1 receptors. Thus, in frontal cortical neurons, sigma-1 receptors appear to facilitate the desensitization of the Ca²⁺ response to NMDA [33]. Attenuation of NMDA-induced calcium responses by sigma ligands in frontal cortical neurons was also observed in a later study, and that study confirmed that sigma ligands shifted the NMDA response from a sustained to a biphasic or transient event [61].

In an interesting study on the sigma-1 receptor agonist igmesine, the effect of intracerebroventricularly administered modulators of calcium influx and mobilization was examined on the reduction of immobilization time caused by igmesine in the forced swimming test. Using chelators of extracellular and intracellular calcium, L- and N-type voltage-dependent calcium channel antagonists and agonists, evidence was obtained that the antidepressant effect of igmesine is dependent not only on rapid Ca²⁺ influx (like that of classical antidepressants), but also on intracellular Ca²⁺ mobilization [153].

Antagonists of voltage-dependent calcium channels such as nimodipine impair the cognitive performance of rodents in various learning tests. Such impairments could be attenuated by pre-administration of the sigma-1 receptor agonists PRE084, and this attenuation could be completely prevented by co-administration of the sigma-1 receptor antagonist BMY14802. Thus, calcium fluxes are implied in memory processes and an impairment of calcium influx through voltage-dependent calcium channels can, at least partially, be overcome by administration of a sigma-1 receptor agonist [99]. Potentiation or attenuation of calcium signaling via sigma-1 receptors (both Ca²⁺ entry at the plasma membrane level via channels and Ca²⁺ mobilization from intracellular stores) may explain why selective sigma-1 receptor agonists can modulate a wide variety of neuronal responses, and be the key mechanism by which sigma-1 receptors affect learning and memory [110].

9. Involvement of sigma-1 receptors in neuronal differentiation and neuroplasticity

Sigma-1 receptors are expressed not only in neurons but also in astrocytes and oligodendrocytes within the brain [35,37]. Overexpression of sigma-1 receptors potentiates nerve growth factor (NGF)-induced neurite outgrowth in PC-12 cells, and this effect can be blocked by sigma-1 receptor antisense [144]. Sigma-1 receptors are strongly upregulated in the corpus callosum of developing brains, particularly in the phase of active myelination [37]. A high expression of these binding sites is observed in oligodendrocytes [127] and Schwann cells [128], suggesting involvement of the sigma-1 receptor in myelination. Knockdown of these receptors by siRNA results in complete inhibition of the differentiation and myelination of oligodendrocyte progenitor cells [37] and prevention of the formation of mature dendritic spines in hippocampal primary neurons [149]. Eliprodil, a neuroprotective drug with a high affinity agonist action at sigma receptors, strongly promotes myelination in neuron–oligodendrocyte cocultures. These data suggest that upregulation of sigma-1 receptors is an important prerequisite for neuronal differentiation, and that sigma-1 receptor agonists like eliprodil may be of therapeutic interest in demyelinating diseases such as multiple sclerosis [22].

Overexpression of sigma-1 receptors promotes lipid reconstitution in the plasma membrane and potentiates raft-residing neurotrophic factors receptors and signal transduction (NGF, EGF, BDNF) [38,145,146,160]. These neurotrophic factor signaling pathways may therefore be involved in the differentiation-promoting effects of sigma-1 receptors. When PC-12 cells are treated with NGF and verbenachalcone, a differentiation enhancer, the sigma-1 receptor belongs to the 10 (out of 10,000) genes showing the strongest upregulation [161]. Since a very high expression of sigma-1 receptors has been noticed in the ventricular zone of young rat brains, where active proliferation and differentiation of cells occurs [37], sigma-1 receptors may not only play an important role in neuroplasticity but may also be involved in neurogenesis. An involvement of sigma-1 receptors in neurogenesis is suggested by the observation that continuous administration of the sigma-1 agonist SA4503 dose-dependently enhances the number of bromodeoxyuridine-positive cells in the subgranular zone of the adult rat hippocampus (by 48% at 3 mg/kg/day and by 94% at 10 mg/kg/day, respectively, after a treatment period of 3 days),
indicating an increased cellular proliferation. Since SA44503 causes parallel increases of hippocampal 5-HT neurotransmission and cell proliferation, the neurotransmitter serotonin may play a central role in the proliferation process [67].

Not only sigma-1 receptor overexpression, but also drug-induced sigma-1 receptor activation results in potentiation of NGF-induced neurite outgrowth. Donepezil, a combined sigma-1 receptor ligand and AChE inhibitor (IC50 values 14.6 nM and 21.5 nM, respectively [59]), potentiates NGF-induced neurite outgrowth in PC-12 cells, and this effect of donepezil can be blocked by the sigma-1 receptor antagonist NE-100 or the inositol 1,4,5-triphosphate (IP3)-receptor antagonist xestospongin C [50], but is not affected by chinolocrotein antagonists (mecamylamine, scopolamine) or cholinomimetic drugs (nicotine, carbachol) [125]. Prysostigmine, an AChE inhibitor without sigma-1 receptor affinity, does not alter NGF-induced neurite outgrowth [50]. The SSRI fluvoxamine (but not the SSRIs sertraline or paroxetine) and the sigma-1 receptor agonist SA44503, PPBP and DHEA-sulfate likewise potentiate neurite outgrowth in PC-12 cells in a concentration-dependent manner, and the effect of these drugs can be blocked by NE-100 or xestospongin C [120]. Since sertraline and fluvoxamine have similar affinities to sigma-1 receptors [119] but only fluvoxamine promotes outgrowth, these data may indicate that sertraline is a sigma-1 receptor antagonist and fluvoxamine a sigma-1 receptor agonist [120]. Specific inhibitors of phospholipase C (PLC), phosphatidylinositol 3-kinase (PI3K), p38 mitogen-activated protein kinase (p38MAPK), c-Jun terminal kinase (JNK), and the Ras/Raf/mitogen-activated protein kinase signaling pathways block the potentiation of NGF-induced neurite outgrowth as well [120]. Apparently, both sigma-1 receptors and IP3 receptors are involved in the potentiation of neurite outgrowth by the test drugs, besides the PLC, PI3K, p38MAPK, JNK and the Ras/Raf/MAPK signaling pathways.

10. Conclusion

Because of the neumodulatory role of sigma-1 receptors, ligands for these binding sites can affect a large variety of cerebral processes. Modification of calcium transients (both by affecting calcium release from intracellular stores and influx of extracellular calcium) and modulation of potassium channel activity via direct protein–protein interaction appear to be key processes underlying the action of sigma-1 receptor ligands. Probably via these mechanisms, several neurotransmitter systems are modulated, particularly the cholinergic and glutamatergic (NMDA-receptor) pathways. The modulatory role of sigma-1 receptors explains why sigma-1 receptor ligands are usually devoid of an effect under control conditions but have striking effects when the normal homeostasis of the organism has been disturbed, e.g. by disease or by a pharmacological challenge. Data from preclinical studies in a large variety of animal models suggests that sigma-1 receptor agonists are promising compounds for the treatment of cognitive dysfunction.

References

[34] Hayashi T, Maurice T, Su TP. Ca(2+) signaling via sigma-1 receptors: novel regulatory mechanism affecting intracellular Ca(2+) concentration. J Pharmacol Exp Ther 2000;293:788–98.
[36] Hayashi T, Su TP. Intracellular dynamics of sigma-1 receptors (sigma-1 binding sites) in NG108-15 cells. J Pharmacol Exp Ther 2003;306:726–33.


Hayashi T, Su TP. The potential role of sigma-1 receptors at galactosylceramide-enriched lipid raft in rat hippocampus. J Physiol 2005;575:315–9.

Hayashi T, Su TP. A novel cognitive enhancer, with sigma-1 receptor agonist properties. Behav Brain Res 1997;83:221–4.


Matsuno K, Senda T, Kobayashi T, Mita S. Involvement of sigma 1 receptor in the modulation of NMDA receptor-stimulated hippocampal cholinergic functions in rats. Brain Res 1995;690:200–6.


by sigma (sigma) receptor ligands involves both sigma1 and sigma2 sites. Br J Pharmacol 1999;127:335–42.


[96] Maurice T, Privat A. Sigma1 (sigma1) receptor agonists and properties that differentiate sigma1 receptor-activated learning in mice. Eur J Pharmacol 1997;328:9–18.


[105] Meunier J, Jeni J, Maurice T. The anti-amnesic and neuroprotective effects of dionepeil against amyloid beta(25–35) peptide-toxicity in mice involve an interaction with the sigma1 receptor. Br J Pharmacol 2006;149:998–1012.


[149] Tsai SY, Hayashi T, Su TP. Hippocampal dendritogenesis and associated anchoring of NMDA and AMPA receptors are controlled by sigma-1 receptors. Int J Neuropsychopharmacol 2006;9:S213 (abstract).


[153] Urani A, Romieu P, Portales-Casamar E, Roman FJ, Maurice T. The antidepressant-like effect induced by the sigma1 (sigma1) receptor agonist igmesine involves modulation of intracellular calcium mobilization. Psychopharmacology (Berl) 2002;163:26–35.


