The role of sigma-1 receptors in the pathophysiology of neuropsychiatric diseases

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Abstract: The endoplasmic reticulum protein sigma-1 receptors, first regarded as opioid receptors and later confused as the phencyclidine (PCP) binding sites of the N-methyl-D-aspartate (NMDA) receptor, are now confirmed to be independent receptors. They are involved in the modulation of various neurotransmitter systems and have a high affinity for diverse classes of psychotropic drugs. Accumulating evidence suggests that the sigma-1 receptors are implicated in higher-ordered brain functions and play important roles in the pathophysiology of neuropsychiatric diseases such as schizophrenia, depression, anxiety disorders, and dementia. Recently, sigma-1 receptors have been shown to function at the molecular level as “receptor chaperones.” This mechanism may unify the explanation of the role of sigma-1 receptors in the pathophysiology of neuropsychiatric diseases. With the development of the positron emission tomography (PET) ligand [¹¹C]SA4503, it has become possible to visualize sigma-1 receptors and estimate the sigma-1 receptor occupancy of drugs in the human brain. This approach may provide additional information on the function of sigma-1 receptors. This article reviews the function of sigma-1 receptors and attempts to reinterpret their role in the pathophysiology of neuropsychiatric diseases based on their new description as “receptor chaperones.”

Keywords: sigma-1 receptor, schizophrenia, major depressive disorder, obsessive-compulsive disorder, Alzheimer's disease, positron emission tomography

Introduction

2007 was a breakthrough year in the research on sigma-1 receptors. Hayashi and Su proposed the novel concept of “receptor chaperones” to explain the physiological roles of sigma-1 receptors.¹ In order to understand the impact of this report, we must first look back on the history of sigma-1 receptor research.

Sigma receptors were first mistakenly proposed to be a subclass of opioid receptors. While investigating the responses of benzomorphans in the nondependent chronic spinal dog, Martin and colleagues² reported that, unlike morphine, which causes analgesic actions, ketocyclazocine and SKF10047 (N-allylnormetazocine) set off different psychological reactions. Taking the initial S of SKF10047, which elicits psychotomimetic effects, and exchanging it for its Greek equivalent, Martin and colleagues gave the name “sigma receptor” to the corresponding subtype opioid receptor.² Subsequent studies revealed that behaviors induced by SKF10047 were resistant to the classical opiate receptor antagonists naloxone³ and naltrexone,⁴ thus differentiating the sigma receptors from classic opiate receptors.

However, because SKF10047 interacts with many binding sites and because its dextrorotatory analogue, (+)-SKF10047 (Figure 1), possesses phencyclidine (PCP)-like

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properties, sigma receptors were next misunderstood as PCP binding sites. The PCP binding site was later found to be an ionophore of the N-methyl-D-aspartate (NMDA) receptor.⁵ Further autoradiographic studies using more selective radioligands demonstrated that sigma receptors and PCP binding sites show different distributions,⁶ leading to the conclusion that the sigma receptor is a unique binding site.⁷

Characteristics of sigma-1 receptors

Binding studies and pharmacological activity studies show that the sigma receptor consists of at least two subtypes, sigma-1 and sigma-2.^{7,8} In 1996, the sigma-1 receptor was successfully cloned and its molecular conformation was revealed.⁹ The sigma-1 receptor is a 223 amino acid protein with two transmembrane domains (Figure 2), and although it

(+)SKF10047

SA4503 (cutamesine)

PRE084

Haloperidol

Rimcazole

BMY14802

Eliprotil (SL-82.0715)

Igmesine

Panamesine (EMD57445)

Figure 1 Chemical structures of sigma-1 receptor ligands.

Figure 2 Predicted structure of sigma-1 receptor. Predicted molecular structure of the sigma-1 receptor. Circles represent amino acids. A slight modification from the figure by Hayashi and colleagues.¹

has no homology to any other mammalian proteins, it shares a 30% identity with a yeast C8–C7 sterol isomerase.⁹ Sigma-1 receptors mainly reside on the endoplasmic reticulum (ER), and they dynamically translocate inside cells.^{10,11} Further studies revealed that sigma-1 receptors are particularly enriched at the mitochondria-associated ER membrane.¹

As mentioned above, Hayashi and Su¹ proposed that sigma-1 receptors function as “receptor chaperones.” In the steady state, sigma-1 receptors form a complex with another molecular chaperone, BiP. By forming this complex, sigma-1 receptors are inhibited from activation. A decrease of Ca²⁺ in the ER causes the sigma-1 receptor to part from the BiP complex, and thus the sigma-1 receptor becomes an activated chaperone. The activated sigma-1 receptor then binds to the inositol 1-4-5-triphosphate (IP₃) receptor. IP₃ receptors are very unstable proteins and are easily degraded by proteasomes, but the binding of sigma-1 receptor stabilizes them. As a result of this stabilization, Ca²⁺ flows into the mitochondria via voltage-dependent anion channels. This inflow of Ca²⁺ into the mitochondria activates the intramitochondrial tricarboxylic acid (TCA) cycle, which induces cell-hypermetabolization, and ultimately results in neuroprotection and neurite outgrowth.^{1,12} Such neuroprotection and neurite outgrowth are thought to contribute to the improvement of various neuropsychiatric diseases (Figure 3). Thus, sigma-1 receptors are assumed to serve as a regulator of adenosine triphosphate (ATP) production and bioenergetics within the cell.¹² The ability to detach BiP from sigma-1 receptors discriminates sigma-1 agonists from antagonists (Table 1).¹

Neuropsychiatric disorders and sigma-1 receptors

We will next discuss the role of the sigma-1 receptors in the pathophysiology of some major neuropsychiatric diseases (Table 2).

Schizophrenia

Schizophrenia is a major psychiatric disorder which shows positive symptoms (eg, hallucinations and delusions), negative symptoms (eg, affective flattening, alogia, or avolition), and cognitive impairments (eg, severe deterioration of concentration and memory). It has been reported that approximately 2.4 million American adults or about 1.1% of the population aged 18 years and older in a given year¹³ have schizophrenia using the DSM-IV classification. Although schizophrenia itself has been recognized for centuries, pharmaceutical treatment only began in the 1950s with the

development of chlorpromazine, which mainly targeted positive symptoms. Following chlorpromazine, many other pharmacological agents were developed, most of which are now grouped as typical antipsychotics. These agents were dopamine D₂ receptor antagonists and although they showed therapeutic performance for positive symptoms, dose-dependent extrapyramidal symptoms (EPS) were inevitable. Atypical antipsychotics with lower rates of EPS were introduced in the 1980s, resulting in a partial recovery of negative symptoms in addition to a decrease in positive symptoms. Despite these advances, however, the rehabilitation rates of schizophrenics are still low.

Because SKF10047 induced psychotomimetic effects, sigma-1 receptors were first considered to be intimately associated with schizophrenia. In fact, there are reports showing a reduction of sigma-1 receptors in the brains of schizophrenic patients postmortem,^{14,15} and the typical and widely used antipsychotic haloperidol (Figure 1) has a very high affinity for sigma-1 receptors.^{3,16} Interestingly, it is also reported that sigma-1 receptors are engaged in modulating NMDA-type glutamate receptors,^{17–19} which might be involved in the pathophysiology of schizophrenia.^{20–26}

Clinical trials with rimcazole, BMY 14802, eliprodil (SL-82.0715) and panamesine (EMD57445) (Figure 1) have been conducted.²⁷ Unfortunately, most of these ligands show poor efficacy for the treatment of schizophrenia, and for acute symptoms their effects can even be negative.²⁷ However, an open label study for eliprodil, performed with chronic schizophrenic patients with predominantly negative symptoms, improved the negative symptoms as assessed by the positive and negative syndrome scale.²⁸ Panamesine improved both positive and negative symptoms,²⁹ but as the metabolite of panamesine was found to have potent antidopaminergic properties which might explain these improving effects, this information must be taken with caution.²⁷

The prominence of cognitive impairments as core symptoms of schizophrenia has recently been reconsidered.³⁰ A number of basic research studies have demonstrated the role of sigma-1 receptors in schizophrenic cognitive impairments. PCP is known to induce negative symptoms and cognitive impairments in healthy individuals, and is therefore used in animal models of schizophrenia. We reported that repeated administration of PCP caused the reduction of sigma-1 receptors in the frontal cortex³¹ and the hippocampus³² in the mouse brain, consistent with a previous report¹⁴ on postmortem brain samples from schizophrenia patients. The PCP-induced cognitive impairments could be improved by subsequent subchronic administration of fluvoxamine but not

Figure 3 Mechanism of action of sigma-1 receptor agonists. Postulated mechanism of sigma-1 receptors.

paroxetine or sertraline.^{31,33} In addition, the selective sigma-1 agonist SA4503 or neurosteroid dehydroepiandrosterone-sulfate (DHEA-S)³³ improved PCP-induced cognitive deficits in mice. These effects were antagonized by coadministration of the selective sigma-1 receptor antagonist NE-100 (Figure 1),³⁴ suggesting that sigma-1 receptor agonism of these drugs might be involved in the mechanism of action. These results indicate that sigma-1 receptor agonists would

be potential therapeutic drugs for the treatment of cognitive impairments in schizophrenia.

Adjunctive medication of fluvoxamine, a sigma-1 receptor agonist (Table 1), has been reported to improve primary negative symptoms in chronic schizophrenia patients who had been treated with antipsychotics.^{35,36} Furthermore, Iyo and colleagues³⁷ reported a case that demonstrated the efficacy of 50 mg/day-fluvoxamine, but not 20 mg/day-paroxetine,

Table I Substances related to sigma-1 receptors¹

Agonist (activation)	Antagonist (inactivation)	No effect
(+) Pentazosine	NE-100	Paroxetine
(+) SKF10047	Haloperidol	Risperidone
Fluvoxamine	Sertraline	Physostigmine
Igmesine	BD1047	
Pregnenolone-S	BD1063	
DHEA-S		
Donepezil		
PPBP		
SA4503		
PRE-048		

Notes: Substances classified based on its action towards the binding of BiP and sigma-1 receptor. Substances which disengage sigma-1 receptors from BiP are agonists.

Abbreviations: DHEA, dehydroepiandrosterone; S, sulfate.

on cognitive deficits in a schizophrenic patient treated with risperidone (no affinity at sigma-1 receptors).³⁸ Therefore, there is need of a further double-blind, placebo-controlled study of the effects of adjunctive fluvoxamine on cognitive impairments in patients with schizophrenia.

There are a few reports indicating that polymorphisms of the sigma-1 receptor gene (SIGMAR1) are associated with schizophrenia. Two functional polymorphisms of SIGMAR1, GC-241-240-TT and Gln2Pro, were identified and reported to have a significant association with schizophrenia.³⁹ Subsequent studies failed to confirm this,^{40,41} but a study by Takizawa and colleagues⁴² using 52-channel near-infrared spectroscopy showed a significant association between the prefrontal hemodynamic response during a verbal fluency task and the Gln2Pro polymorphism of the sigma-1 receptor gene in schizophrenia patients.

Major depressive disorder

Major depressive disorder is a common mood disorder characterized by depressed mood, insomnia, irritation, and cognitive deficits, and in severe cases can lead to suicide. Major depressive disorder is the leading cause of disability in the United States for ages 15 to 44 years⁴³ and affects approximately 14.8 million American adults or about 6.7% of the USA population aged 18 years and older in a given year.⁴⁴

A relationship between sigma-1 receptors and depression was first identified by Matsuno and colleagues⁴⁵ using the forced swimming test (FST), which is a standard animal model of depression. Sigma-1 ligands such as igmesine⁴⁶ and SA4503⁴⁷ (Figure 1) show antidepressive effects in the FST, and these effects are antagonized by the sigma-1

antagonists BD1047 or NE-100 (Figure 1). Interestingly, the antidepressant-like effect of SA4503 was achieved following a single administration of the drug. Subsequently, the rapid antidepressant-like action of SA4503 was replicated by different sigma-1 receptor agonists.^{48,49} Furthermore, electrophysiological studies demonstrated a rapid antidepressant-like action for sigma-1 receptor agonists.⁵⁰ In addition, sigma-1 receptor knock-out mice show longer immobility time in the FST, indicating the depression-like phenotype of the mice.⁵¹ We have reported that fluvoxamine, but not sertraline or paroxetine, potentiated nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells.⁵² Other sigma-1 receptor agonists such as SA4503, 4-phenyl-1-(4-phenylbutyl)piperidine (PPBP), and DHEA-S (Figure 1) also exhibited the potentiating effect, and all the outgrowth effects were also antagonized by co-incubation with NE-100.⁵² This finding is consistent with the sigma-1 receptor's "receptor chaperone" mechanism, which ultimately results in neurite outgrowth (Figure 3). Taken together, these results suggest that sigma-1 receptor agonists have rapid antidepressant-like actions,¹² unlike existing antidepressants which have a delayed onset of action of 2–6 weeks. A phase II study of SA4503 (cutamesine) in patients with major depression is currently underway.

Neurosteroids are hormones produced in the central and peripheral neurons, and were first reported by Baulieu.⁵³ It was shown that the brain concentrations of the neurosteroids DHEA, DHEA-S, pregnenolone, and pregnenolone sulfate (Figure 1) were far greater than those found in the circulation. Furthermore, their concentrations in the brain remained high after adrenalectomy and orchietomy, suggesting that these steroids did not originate from steroidogenic tissue but rather originated through local brain synthesis. As these neurosteroids have moderate affinity towards sigma-1 receptors, they are considered to be endogenous ligands. Some neurosteroids show antidepressive activity in the FST, and NE-100 has been shown to antagonize the improvements,^{54,48} indicating that the antidepressive effect of these drugs is brought on by sigma-1 receptors. In consideration of these results, it is likely that sigma-1 receptor agonists would be effective as rapid acting antidepressant drugs for major depression.^{55–59}

Psychotic (or delusional) major depression is a challenging disease which has, in addition to depressive symptoms, psychotic delusions such as delusions of poverty or sin and has significantly higher mortality than nonpsychotic major depression.^{60,61} This condition is associated with much greater dysfunction of cognitive ability than major depression.

Table 2 Summarization of psychiatric diseases and its association with sigma-1 receptors

Mental disorders	Main related substances		Associating events
Schizophrenia	Haloperidol Eliprodil (SL-82.0715) Fluvoxamine	Preclinical	<ul style="list-style-type: none"> • Sigma-1 ligands modulate NMDA receptors which effect dopamine regulation^{17–19}
		Clinical	<ul style="list-style-type: none"> • Reduction of sigma-1 receptors in the postmortem schizophrenic brain^{14,15} • Adjunctive medication of sigma-1 ligands effective for cognitive deficits of schizophrenia^{35–37}
Major depressive disorder	Fluvoxamine SA4503 Igmesine (JO-1784) Neurosteroids	Preclinical	<ul style="list-style-type: none"> • Sigma-1 ligands show antidepressive effects in the forced swimming test^{45–49} • Neurosteroids, considered as endogenous sigma-1 ligands, show antidepressive effects^{48,54}
		Clinical	<ul style="list-style-type: none"> • Psychotic major depression is improved by fluvoxamine monotherapy^{62–64,66}
Obsessive–compulsive disorder	Fluvoxamine	Preclinical	<ul style="list-style-type: none"> • Fluvoxamine improves marble-burying behavior in mice through sigma-1 receptor activity⁷⁵
		Clinical	<ul style="list-style-type: none"> • Fluvoxamine effective for obsessive-compulsive disorder⁷² • Fluvoxamine enhances the effect of cognitive behavioral therapy^{78,79}
Alzheimer's disease	Donepezil PRE-048	Preclinical	<ul style="list-style-type: none"> • Donepezil show neuroprotective properties against Aβ_{25–35} peptide-induced toxicity⁸² • Donepezil show anti-amnesic effects which are antagonized by sigma-1 antagonists⁸²
		Clinical	<ul style="list-style-type: none"> • Decrease of sigma-1 receptors in the Alzheimer's disease brain^{85,86}

Note: Summarized table of psychiatric diseases and relating substances and events regarding the sigma-1 receptor.

Abbreviation: NMDA, N-methyl-D-aspartate.

The typical treatment for psychotic major depression is to administer a combination of antipsychotics and antidepressants. However, this approach may lead to significant side effects, including EPS.

Interestingly, there are multiple reports showing that monotherapy with the selective serotonin reuptake inhibitor (SSRI) fluvoxamine was effective for the treatment of this disorder.^{62–64} Another SSRI, paroxetine, had a lesser effect.⁶⁵ The reason underlying the difference in efficacy between these two SSRIs is currently unknown. Unlike paroxetine, which has an inhibition constant (K_i) of 1893 nM, fluvoxamine is a potent sigma-1 receptor agonist with a K_i of 36 nM,⁶⁶ suggesting that sigma-1 receptors are involved in the mechanisms of fluvoxamine's action.⁶⁷ In addition, Shirayama and Hashimoto⁶⁸ reported a case showing that fluvoxamine monotherapy was effective in a Japanese female patient with psychotic depression. Based on all these findings, it has been proposed that sigma-1 receptors may be implicated in the efficacy of fluvoxamine for psychotic major depression.^{69,70} These reports suggest that fluvoxamine monotherapy could be a good alternative approach for the

treatment of psychotic depression, since it decreases the risk of EPS by obviating the need for antipsychotic drugs. Nevertheless, further detailed, double-blind studies will be needed to clarify the role of sigma-1 receptors in the efficacy of fluvoxamine for psychotic depression.

Obsessive–compulsive disorder

Obsessive–compulsive disorder (OCD) is an anxiety disorder characterized by obsessions and compulsions. Obsessions are recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress. Compulsions are repetitive behaviors (eg, hand washing, ordering, checking) or mental acts (eg, praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.⁷¹ These acts are often performed in the hope of preventing or reducing anxiety or distress.

SSRIs are the first choice pharmaceutical treatment for OCD, and fluvoxamine has been tested in several dou-

ble-blind, placebo-controlled and active-comparison studies. It was demonstrated that fluvoxamine had equal efficacy to clomipramine (a tricyclic antidepressant with potent serotonin reuptake inhibition) and other SSRIs (paroxetine and citalopram).⁷² As a result, fluvoxamine was the first SSRI to be approved for OCD.⁷³ An extended release type of fluvoxamine, fluvoxamine CR, has also been considered effective for OCD, and allows a higher starting dose without increasing the occurrence of side effects.⁷⁴

In a preclinical study, Egashira and colleagues⁷⁵ demonstrated that fluvoxamine ameliorated the marble-burying behavior in mice, which is considered to be a potential model of OCD, and that these ameliorating effects were antagonized by the sigma-1 receptor antagonist BD-1047 or BD-1063 (Figure 1) but not by the sigma-2 receptor antagonist SM-21. In the case of paroxetine administration, on the other hand, the marble-burying behavior was ameliorated, but the improvements were unaffected by BD-1047 or BD-1063.⁷⁵ These results strongly indicate that fluvoxamine has an additional therapeutic effect for OCD through sigma-1 receptors, which in turn indicates that sigma-1 receptors may be involved in the psychopathological symptoms of OCD.

Cognitive behavioral therapy (CBT) is effective for the treatment of OCD.^{76,77} Two placebo-controlled studies have reported that fluvoxamine enhances the effect of CBT.^{78,79} This is consistent with the multiple reports of fluvoxamine improving cognitive deficits via sigma-1 receptors. These reports suggest that sigma-1 receptors may be involved in the pathology of OCD, although further studies will be needed to confirm this.

Alzheimer's disease

Alzheimer's disease (AD) is a progressive and fatal neurodegenerative disorder mainly manifested by cognitive and memory deterioration.⁸⁰ Research advances have revealed that the molecular pathogenesis of this disease principally involves amyloid β ($A\beta$) plaques and hyperphosphorylated tau tangles.⁸¹

Donepezil (Figure 1), an acetylcholinesterase (AChE) inhibitor, is the most widely prescribed drug for AD.⁸¹ Donepezil was found to have neuroprotective properties against $A\beta_{25-35}$ peptide-induced toxicity in mice.⁸² In the same report, donepezil and the sigma-1 agonist PRE-048 (Figure 1), as well as the cholinesterase inhibitors tacrine, rivastigmine, and galantamine, showed anti-amnesic effects. But only the effects of PRE-048 and donepezil were antagonized by the sigma-1 receptor antagonist BD-1047 (Figure 1).⁸² Also, when administered before $A\beta_{25-35}$ injection, only

PRE-048 and donepezil showed neuroprotective effects. This was confirmed by the blocking of lipid peroxidation and improvements of learning deficits, effects again inhibited by BD-1047. Administration of PRE-048 and donepezil after $A\beta_{25-35}$ injection induced complete neuroprotection, whereas the other cholinesterase inhibitors showed only partial effects.⁸² Taken together, these findings suggest that the beneficial effects of donepezil occur via sigma-1 receptors and that the neuroprotection conferred by pre-administration of donepezil through sigma-1 receptors may lead to means of AD prevention.

We previously reported that donepezil, but not physostigmine, significantly potentiated NGF-induced neurite outgrowth in PC12 cells in a concentration-dependent manner, and that the effect of donepezil could be antagonized by NE-100.⁸³ Furthermore, we reported that donepezil, but not physostigmine, significantly improved PCP-induced cognitive impairments in mice, and that the effect of donepezil could be antagonized by co-administration of NE-100.³² Our positron emission tomography (PET) study demonstrated that donepezil bound to sigma-1 receptors in the human brain in a dose-dependent manner.⁸⁴ Therefore, it is likely that sigma-1 receptors are involved in the mechanism of the pharmacological action of donepezil in the human brain.

A postmortem has revealed that the density of sigma-1 receptors is reduced in the hippocampus of patients with AD.⁸⁵ Mishina and colleagues⁸⁶ reported in a study using [¹¹C]SA4503 and PET that AD patients had a lower density of sigma-1 receptors than age-matched controls. A further PET study using drug-untreated patients with AD would be of interest, because some patients in this report were receiving donepezil treatment.

PET study of sigma-1 receptors in the human brain

PET is a noninvasive imaging technique which produces functional process images by detecting gamma rays emitted from positron emitting tracers. Because the main positron-emitting radionuclides (¹¹C, ¹³N, ¹⁵O, ¹⁸F) used in PET are elements found within a living organism, PET is useful for quantitative measurement of physiological and biochemical information. PET can also measure neural receptors in the brain quantitatively and can calculate the receptor occupancy of target drugs. Therefore, in order to unravel the relation between sigma-1 receptors and various neuropsychiatric diseases, PET imaging should be used to image the cerebral distribution of sigma-1 receptors and

to examine the disease-related changes in the distribution of sigma-1 receptors.

Development of PET tracers to measure sigma-1 receptors began in the 1980s, and it was subsequently established that ^{11}C -labeled 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine (^{11}C]SA4503) is useful for this purpose.^{87–90} Ishiwata and colleagues⁹⁰ reported a high occupancy of sigma-1 receptors (approximately 80%) as well as dopamine D_2 receptors (approximately 60%) in the human brain after a single oral administration of haloperidol (3 mg), suggesting that a PET study with ^{11}C]SA4503 can be used for evaluating the sigma-1 receptor occupancy by therapeutic drugs in the human brain. Subsequently, we have used ^{11}C]SA4503-PET to evaluate successfully the sigma-1 receptor occupancy by fluvoxamine⁹¹ and donepezil,⁸⁴ demonstrating that fluvoxamine and donepezil

bind to sigma-1 receptors in the human brain at therapeutic doses (Figures 4 and 5). These findings suggest that sigma-1 receptors may be involved in the mechanism of action of fluvoxamine and donepezil. Finally, it is very important to investigate whether sigma-1 receptor density is altered in the brains of patients with schizophrenia, major depression, OCD, or AD using ^{11}C]SA4503-PET.

Conclusion

As described above, the unique ER protein sigma-1 receptors are assumed to serve as a regulator of ATP production and bioenergetics within the cell,^{1,12} and sigma-1 receptors may play a key role in the pathophysiology of some neuropsychiatric diseases. Furthermore, sigma-1 receptor agonists have been implicated in the enhancement of neuroplasticity and cognitive functioning. The clinical potential of sigma-1

Figure 4 The ^{11}C]SA4503-PET (positron emission tomography) images of before and after taking a selective serotonin reuptake inhibitor (SSRI). Volume of distribution images of ^{11}C]SA4503-PET before and after a single oral administration of an SSRI. The upper pair represents images at baseline (left) and at paroxetine (20 mg)-loading (right) in the same subject. The lower pair shows images at baseline (left) and fluvoxamine (200 mg)-loading (right) in another subject. Note that while paroxetine does not effect ^{11}C]SA4503 binding, fluvoxamine obstructs the ^{11}C]SA4503 binding because fluvoxamine itself binds to sigma-1 receptors.

Figure 5 The [^{11}C]SA4503-PET images of before and after taking donepezil. Representative images of the volume of distribution of [^{11}C]SA4503-PET before (left) and after (right) a single oral administration of donepezil (10 mg) in a healthy subject.

receptor agonists is only just beginning to be explored. The primary therapeutic targets of sigma-1 receptor agonists in ongoing research include schizophrenia, major depression, OCD, and AD.

Disclosures

The authors report no conflicts of interest in this work.

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