High Occupancy of Sigma-1 Receptors in the Human Brain after Single Oral Administration of Fluvoxamine: A Positron Emission Tomography Study Using \[^{11}\text{C}^\]
SA4503

Masatomo Ishikawa, Kiichi Ishiwata, Kenji Ishii, Yuichi Kimura, Muneyuki Sakata, Mika Naganawa, Keiichi Oda, Ryousuke Miyatake, Mihisa Fujisaki, Eiji Shimizu, Yukihiko Shirayama, Masaomi Iyo, and Kenji Hashimoto

**Background:** Sigma-1 receptors might be implicated in the pathophysiology of psychiatric diseases, as well as in the mechanisms of action of some selective serotonin reuptake inhibitors (SSRIs). Among the several SSRIs, fluvoxamine has the highest affinity for sigma-1 receptors (Ki = 36 nM), whereas paroxetine shows low affinity (Ki = 1893 nM). The present study was undertaken to examine whether fluvoxamine binds to sigma-1 receptors in living human brain.

**Methods:** A dynamic positron emission tomography (PET) data acquisition using the selective sigma-1 receptor ligand \[^{11}\text{C}^\]
SA4503 was performed with arterial blood sampling to evaluate quantitatively the binding of \[^{11}\text{C}^\]
SA4503 to sigma-1 receptors in 15 healthy male volunteers. Each subject had two PET scans before and after randomly receiving a single dose of either fluvoxamine (50, 100, 150, or 200 mg) or paroxetine (20 mg). The binding potential of \[^{11}\text{C}^\]
SA4503 in 9 regions of the brain was calculated by a 2-tissue 3-compartment model. In addition, we examined the effects of functional polymorphisms of the sigma-1 receptor (SIGMAR1) gene on the binding potential of \[^{11}\text{C}^\]
SA4503.

**Results:** Fluvoxamine bound to sigma-1 receptors in all brain regions in a dose-dependent manner, whereas paroxetine did not bind to sigma-1 receptors. However, there was no association between the SIGMAR1 gene polymorphism GC-241-240TT and binding potential.

**Conclusions:** The study demonstrated that fluvoxamine bound to sigma-1 receptors in living human brain at therapeutic doses. These findings suggest that sigma-1 receptors may play an important role in the mechanism of action of fluvoxamine.

**Key Words:** Fluvoxamine, occupancy, paroxetine, PET, sigma-1 receptor, SSRI

Selective serotonin reuptake inhibitors (SSRIs) have emerged as a major therapeutic advance in psychopharmacology. SSRIs are the treatment of choice for many indications, including major depressive disorder, dysthymia, obsessive-compulsive disorder, and obsessive-compulsive disorder spectrum disorders (which include panic disorder, eating disorders, and others), because of their efficacy, safety profile, tolerability, and low toxicity in case of overdose, as well as patient compliance (1,2). Although all the SSRIs share the blockade of the serotonin transporters that leads to elevation of serotonin levels throughout the central nervous system, it is well known that their pharmacology is quite heterogeneous (3–11).

Sigma-1 receptors act as specific binding sites in the central nervous system, and they exert a potent modulation on a number of neurotransmitter systems, including the glutamatergic, noradrenergic, dopaminergic, serotonergic and cholinergic systems. Several lines of evidence suggest that sigma-1 receptors play a role in the pathophysiology of responses to stress and psychiatric diseases, including major depression, schizophrenia, cognition, and addiction (12–17). Cell biologically, sigma-1 receptors mainly reside on the endoplasmic reticulum and regulate Ca\(^{2+}\) signaling (18). Furthermore, sigma-1 receptors form a complex with the cytoskeletal adaptor protein ankyrin, and with stimulation to the sigma-1 receptor, it translocates to nuclear membranes and plasma membranes, suggesting that sigma-1 receptors have an important role in neuroplasticity (19). Narita et al. (3) reported that some SSRIs possess high to moderate affinities for sigma-1 receptors in rat brain. The rank order of affinity for SSRIs for sigma-1 receptors is as follows: fluvoxamine (Ki = 36 nM) > sertraline (Ki = 57 nM) > fluoxetine (Ki = 120 nM) > citalopram (Ki = 292 nM). In contrast, paroxetine (Ki = 1893 nM) has low affinity for sigma-1 receptors (3). Thus, it seems that sigma-1 receptors may play a role in the mechanism of action of some SSRIs, such as fluvoxamine (3,15,20).

Positron emission tomography (PET) is the most effective technique to estimate the receptor occupancy rates of drugs in human brain (21,22). Recently, it has been demonstrated that \[^{11}\text{C}^\]
SA4503 is a selective PET ligand for sigma-1 receptor in the brain (23–26). SA4503 has an affinity of approximately 17.4 nM (IC\(_{50}\)) for the sigma-1 receptor, which is about 100 times higher than those for sigma-2, \(\alpha_1\)-adrenergic, dopamine D\(_2\), serotonin (5-HT\(_1\))\(_{AA}\), 5-HT\(_2\), histamine H\(_1\), muscarinic M\(_1\), and muscarinic M\(_2\) receptors, and has no affinity for other 29 receptors, ion channels, and second messenger systems (27). The inhibition curves of SA4503 for \[^{1}\text{H}^\] (+)-pentazocine binding were shifted to the...
right in the presence of GTPγS, as similar to those of sigma-1 receptor agonists ([+]-3-PPP and (+)-pentazocine) (27). In addition, similar to sigma-1 receptor agonist ([+]-3-PPP and (+)-pentazocine), SA4503 significantly increased the Kd value, but not the Bmax value, for specific [3H] (+)-pentazocine binding to sigma-1 receptors (27). These findings suggest that SA4503 is a sigma-1 receptor agonist (27). Binding of [11C]SA4503 in the brains of patients with Alzheimer’s or Parkinson’s disease has been shown to be lower than in normal controls (15,28). Furthermore, Ishiwata et al. (29) reported a high occupancy of sigma-1 receptors (approximately 80%) as well as dopamine D2 receptors (approximately 60%) in human brain after a single oral administration of the typical antipsychotic drug haloperidol (3 mg), suggesting that PET study using [11C]SA4503 can be used for evaluating the sigma-1 receptor occupancy rates by therapeutic drugs in human brain (29).

The purpose of this study was to determine whether two SSRIs, fluvoxamine and paroxetine, bind to sigma-1 receptors in human brain by using [11C]SA4503 and PET. In addition, we examined the effects of polymorphisms of the sigma-1 receptor (SIGMAR1; OMIM No. 601978) gene on the binding potential of [11C]SA4503 in human brain, since polymorphisms (T-485A and GC-241-240TT; rs1799729) in the SIGMAR1 gene have been shown to be functional polymorphisms (30).

Methods and Materials

Subjects

This study was approved by the Ethical Committee of Tokyo Metropolitan Institute of Gerontology and the Ethics Committee of Chiba University Graduate School of Medicine. Fifteen healthy male volunteers participated in the study (mean age = 54.7 years; SD = 4.6, range = 28–41). Written informed consent was obtained from each subject after the procedures had been fully explained. None of the subjects had any neurological or psychological findings, or showed any abnormalities in the brain magnetic resonance imaging (MRI) scan taken between the two PET scans. None had been receiving any medications of any kind. None had a history of alcoholism.

[11C]SA4503 and PET

Each volunteer participated in two [11C]SA4503-PET scans, one before and one after oral administration of an SSRI. The SSRI was administered within 5 min after the end of the first PET scan. The second PET scan took place 4–4.5 hours after taking the SSRI to achieve an adequate level of drug concentration in blood. It has been reported that after oral administration of a single dose of fluvoxamine (50 mg) in healthy subjects, the concentration in blood reaches its peak in approximately 5–6 hours (31,32). Accordingly, we collected blood samples just before tracer injection of the second PET scan to monitor the concentration of fluvoxamine. The concentration of fluvoxamine in blood was measured by liquid chromatography followed by tandem mass spectrometry.

The volunteers were randomly administered either fluvoxamine (50, 100, 150 or 200 mg, n = 3; Lavox (Astellas Ltd, Tokyo, Japan) or paroxetine (20 mg, n = 3; Paxil (GlaxoSmithKline Ltd, Tokyo, Japan). All drug tablets were sealed in the same nondecript capsule so that both the volunteers and administrator would be blind to the contents. PET was performed at the Positron Medical Center, Tokyo Metropolitan Institute of Gerontology with a SET 2400W scanner (Shimadzu Co., Tokyo, Japan).

Data Analysis

Image manipulations were carried out on an O2 work station (Silicon Graphics Inc., Mountain View, California), using the medical image processing application package “Dr. View,” version 5.2 (AJS Co. Ltd., Tokyo, Japan). Regions of interest were defined over the frontal, temporal, parietal, occipital, and anterior cingulate cortices, head of the caudate nucleus, putamen, thalamus, and cerebellum with reference to the coregistered MRI, which served as an anatomical guide. Binding of [11C]SA4503 to sigma-1 receptors was calculated as the binding potential by methods described elsewhere (34). Briefly, binding potentials were computed using a 2-tissue 3-compartment model (35). Sigma-1 receptor occupancy (%) by SSRI was calculated for each region of interest as 100 × [binding potential at baseline–binding potential at SSRI-loading]/binding potential at baseline. Images of the distribution volumes of [11C]SA4503 were calculated using the Logan plot method (34,36).

The relationship between sigma-1 receptor occupancy and the dose or blood concentration of fluvoxamine was modeled by the equation \( \text{Occ} = a \cdot (F/(F + ED50)) \), where Occ refers to occupancy, F refers to dose or blood level of fluvoxamine, a is the maximal receptor occupancy and ED50 is the blood fluvoxamine level resulting in 50% maximal receptor occupancy.

Genotype Analysis

The genotypes of the T-485A and GC-241-240TT in the 5’ untranslated region of the SIGMAR1 gene was analyzed in all volunteers according to methods previously described (30,37).

Statistical Analysis

The data were the mean ± SD. Statistical analysis was performed by using the software package SPSS (SPSS 12.0J; SPSS, Inc., Tokyo, Japan). The dose-dependent relationship was evaluated by one-way analysis of variance with contrast (polynomial). The relationship between the binding potential at baseline
and genotype of the SIGMAR1 gene was analyzed by one-way analysis of variance. Significance for the results was set at $p < .05$.

**Results**

Radioactivity was distributed throughout the human brain after intravenous administration of $[^{11}C]$SA4503. Representative parametric images of the distribution volume of $[^{11}C]$SA4503 at baseline are shown with corresponding MRI images in Figure 1. These results show that sigma-1 receptors are concentrated in brain areas of the limbic system, including areas involved in motor function, sensory perception, and endocrine function, consistent with the previous reports (29,34). Representative images of the distribution volume of $[^{11}C]$SA4503 in the fluvoxamine- and paroxetine-loading conditions are shown in Figure 2. A single administration of fluvoxamine (200 mg), but not paroxetine (20 mg), markedly decreased the distribution volume of $[^{11}C]$SA4503 (Figure 2). Table 1 shows the binding potentials and occupancy rates in 9 brain regions. $[^{11}C]$SA4503 bound throughout the brain, and the cerebellum showed the highest binding potential.

We analyzed whether the effects of fluvoxamine on occupancy of sigma-1 receptors were dose-dependent. Analysis using contrast (polynomial) showed that fluvoxamine significantly and dose-dependently bound to sigma-1 receptors in the frontal cortex ($p < .021$), parietal cortex ($p < .024$), occipital cortex ($p < .011$), head of the caudate nucleus ($p < .012$), thalamus ($p < .008$), and cerebellum ($p < .037$). The dose-dependency also seemed to be operative at the temporal cortex ($p < .069$), anterior cingulate gyrus ($p < .073$), and putamen ($p < .067$), but the correlation at these sites was not statistically significant. There were significant correlations between the blood concentration of fluvoxamine and occupancy in the brain regions (temporal cortex: $r = .62, p < .05$; parietal cortex: $r = .70, p < .05$; occipital cortex: $r = .63, p < .05$; head of the caudate nucleus: $r = .70, p < .05$; putamen: $r = .67, p < .05$; thalamus: $r = .62, p < .05$; cerebellum: $r = .77, p < .01$). There were weak correlations between the blood concentration of fluvoxamine and occupancy in the other two regions (frontal cortex: $r = .54, .05 < p < .1$; cingulate gyrus: $r = .56, .05 < p < .1$). Figure 3 shows representative data for the parietal cortex and cerebellum. There were statistically significant correlations between the sigma-1 receptor occupancy and dose or blood concentration of fluvoxamine in both these brain regions (Figure 3).

Next, we examined whether the SIGMAR1 gene polymorphisms affect the binding potential of sigma-1 receptors in human brain. However, all subjects showed TT genotype at the T-485A site. As for the GC-241-240TT polymorphism, 8 subjects had GC/GC genotype, and 5 subjects had GC/TT genotype, and 2 subjects had TT/TT genotype. There was no association between GC-241-240TT polymorphisms and the baseline binding potentials of sigma-1 receptors in any of the brain regions examined (Supplement 1).

**Discussion**

The major finding of this study is that, after a single oral administration, fluvoxamine bound to sigma-1 receptors in the living human brain in a dose-dependent manner. To our knowledge, this is the first report demonstrating that fluvoxamine binds to sigma-1 receptors in the living human brain at therapeutic doses, which is consistent with the previous report using rat brain (3). Suhara et al. (38) reported a high occupancy (approximately 80%) of serotonin transporters in healthy subjects after a single oral administration of fluvoxamine (50 mg). These results suggest that, at therapeutic doses, fluvoxamine binds to sigma-1 receptors as well as serotonin transporters in the human brain. Taken together, these results suggest that sigma-1 receptors may be involved in the mechanism of the action of fluvoxamine.

A recent study demonstrated that cognitive deficits induced in mice by the N-methyl-D-aspartate receptor antagonist phenycyclidine (PCP) could be ameliorated by subsequent subchronic administration of fluvoxamine, and that the effects of fluvoxamine could be antagonized by co-administration of the selective sigma-1 receptor antagonist NE-100 (20). Furthermore, the selective sigma-1 receptor agonist SA4503 and the endogenous sigma-1 receptor agonist dehydroepiandrosterone sulphate could improve PCP-induced cognitive deficits in mice, and the efficacy of SA4503 and dehydroepiandrosterone-sulphate on PCP-inhibit...
duced cognitive deficits was also antagonized by co-administration of NE-100 (20). These findings suggest that the agonistic activity of fluvoxamine at sigma-1 receptors could be implicated in the mechanisms of action of fluvoxamine (20). Therefore, the agonistic property of fluvoxamine at sigma-1 receptors may suggest that this drug has potential for the treatment of cognitive deficits in depressive and schizophrenic patients.

Mood disorders, including major depressive disorder and bipolar disorder, possess cognitive impairment in the center of their psychopathology. There is a hypothesis that cognitive dysfunction remains after remission, especially in manic bipolar disorder (39), and leads to poor social outcome. As suggested, fluvoxamine may have a potential for treating cognitive deficits through its action against sigma-1 receptors, it being an antidepressant, fluvoxamine may be a useful prescription for mood disorders having cognitive impairment.

An adjunct medication is often added to antipsychotic treatment regimens to improve the response of negative symptoms and cognitive deficits in schizophrenia. Some SSRIs, such as fluvoxamine and fluoxetine, can ameliorate primary negative symptoms in chronic schizophrenic patients (40,41). Currently, the precise mechanisms underlying the efficacy of fluvoxamine on negative symptoms is unclear. However, it is possible that sigma-1 receptors play a role in the mechanism of the action of fluvoxamine, although further study will be needed to confirm this. Taken together, these results also suggest that augmentation with sigma-1 receptor agonists such as fluvoxamine could be a useful addition to the treatment of schizophrenic patients with persistent negative symptoms and cognitive deficits.

Psychotic major depression is a difficult-to-treat illness that is associated with high functional impairment and significantly higher mortality than nonpsychotic major depression (42,43). Interestingly, monotherapy of fluvoxamine has been proven effective against both the psychotic and depressive symptoms of this disorder (44–46). In contrast, a monotherapy of paroxetine did not show equal efficacy as fluvoxamine (47). Based on these findings, it has been recently proposed that this efficacy of fluvoxamine might be due to its specific affinity to sigma-1 receptors in the brain (48,49), suggesting that sigma-1 receptors play a role in psychotic major depression. Therefore, it may be interesting to study whether the binding of $[^{11}\text{C}]\text{SA4503}$ to sigma-1 receptors in the brain is altered in patients with psychotic major depression.

Miyatake et al. (30) reported functional polymorphisms (T-485A) in the promoter region of the SIGMAR1 gene. In this study, we found that there was no association between the SIGMAR1 genotype and the binding potentials of $[^{11}\text{C}]\text{SA4503}$ in any of the regions of the brain in healthy male subjects. These findings suggest that the SIGMAR1 gene polymorphism GC-241-240TT may not contribute to differences in the sigma-1 receptors in the human brain, although a further study using a larger sample will be necessary.

In conclusion, the present study demonstrates that fluvoxamine binds to sigma-1 receptors in the human brain at therapeutic

---

**Table 1.** Binding potential of $[^{11}\text{C}]\text{SA4503}$ and occupancy (%) of selective serotonin reuptake inhibitors in the human brain regions

<table>
<thead>
<tr>
<th></th>
<th>Frontal Cortex</th>
<th>Temporal Cortex</th>
<th>Parietal Cortex</th>
<th>Occipital Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>SSRI</td>
<td>Baseline</td>
<td>SSRI</td>
</tr>
<tr>
<td><strong>F50</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding potential (%)</td>
<td>15.9±5.2</td>
<td>19.5±6.1</td>
<td>15.3±4.3</td>
<td>14.7±4.8</td>
</tr>
<tr>
<td>Occupancy (%)</td>
<td>10.0±3.0</td>
<td>14.0±6.0</td>
<td>9.57±3.0</td>
<td>10.1±4.5</td>
</tr>
<tr>
<td><strong>F100</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding potential (%)</td>
<td>11.7±3.0</td>
<td>14.3±2.6</td>
<td>13.6±1.7</td>
<td>12.9±0.9</td>
</tr>
<tr>
<td>Occupancy (%)</td>
<td>6.56±0.1</td>
<td>8.93±2.7</td>
<td>7.10±1.2</td>
<td>6.69±0.8</td>
</tr>
<tr>
<td><strong>F150</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding potential (%)</td>
<td>20.9±3.7</td>
<td>26.9±4.9</td>
<td>20.6±1.9</td>
<td>19.2±5.3</td>
</tr>
<tr>
<td>Occupancy (%)</td>
<td>7.50±1.2</td>
<td>10.0±1.0</td>
<td>7.39±0.5</td>
<td>6.86±0.3</td>
</tr>
<tr>
<td><strong>F200</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding potential (%)</td>
<td>17.0±5.1</td>
<td>20.8±7.0</td>
<td>16.7±4.4</td>
<td>15.0±6.0</td>
</tr>
<tr>
<td>Occupancy (%)</td>
<td>6.35±0.1</td>
<td>9.89±2.9</td>
<td>6.27±0.4</td>
<td>5.18±1.0</td>
</tr>
<tr>
<td><strong>P20</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding potential (%)</td>
<td>16.5±2.9</td>
<td>20.9±5.6</td>
<td>18.4±3.6</td>
<td>15.6±3.5</td>
</tr>
<tr>
<td>Occupancy (%)</td>
<td>17.1±1.6</td>
<td>20.6±1.2</td>
<td>15.7±2.2</td>
<td>14.8±3.0</td>
</tr>
</tbody>
</table>

Value are the mean ± SD of three subjects.

F50, Fluvoxamine (50 mg); F100, fluvoxamine (100 mg); F150, fluvoxamine (150 mg); F200, fluvoxamine (200 mg); P20, paroxetine (20 mg); SSRI, fluvoxamine or paroxetine.

---

**Figure 3.** Correlations between the sigma-1 receptor occupancy and dose or blood concentration of fluvoxamine in the parietal cortex and cerebellum. The colors of the points correspond to the dose administered.
doses. These findings suggest that sigma-1 receptors may play an important role in the mechanism of action of fluvoxamine.

This study was supported in part by a grant from the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation, Japan (to KH and MI). Hashimoto reports having received the speakers’ bureau honoraria from Solvay Pharmaceuticals. Drs. Ishikawa, Ishiwata, Ishii, Kimura, Sakata, Naganawa, Oda, Miyatake, Fujisaki, Shimizu, Shirayama, and Iyo report no competing interests.

We thank Dr. Masaya Hashimoto and Ms. Hiroko Tsukinari for technical assistance.

Supplementary material cited in this article is available online.


www.sobp.org/journal

**Table 1.** (continued)

<table>
<thead>
<tr>
<th>Anterior Cingulate Gyrus</th>
<th>Head of Caudate Nucleus</th>
<th>Putamen</th>
<th>Thalamus</th>
<th>Cerebellum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>SSRI</td>
<td>Baseline</td>
<td>SSRI</td>
<td>Baseline</td>
</tr>
<tr>
<td>18.3 ± 6.1</td>
<td>11.5 ± 2.6</td>
<td>13.8 ± 3.8</td>
<td>9.32 ± 2.2</td>
<td>14.1 ± 4.3</td>
</tr>
<tr>
<td>34.0 ± 17.6</td>
<td></td>
<td>31.2 ± 11.2</td>
<td></td>
<td>34.0 ± 8.8</td>
</tr>
<tr>
<td>15.3 ± 4.0</td>
<td>8.38 ± 1.4</td>
<td>12.3 ± 0.8</td>
<td>6.19 ± 0.3</td>
<td>12.6 ± 1.5</td>
</tr>
<tr>
<td>40.1 ± 28.9</td>
<td></td>
<td>49.6 ± 1.9</td>
<td></td>
<td>51.7 ± 4.0</td>
</tr>
<tr>
<td>22.2 ± 3.0</td>
<td>9.23 ± 1.6</td>
<td>17.4 ± 0.4</td>
<td>6.05 ± 2.3</td>
<td>18.6 ± 2.3</td>
</tr>
<tr>
<td>58.1 ± 10.0</td>
<td></td>
<td>65.1 ± 14.2</td>
<td></td>
<td>56.7 ± 12.1</td>
</tr>
<tr>
<td>19.9 ± 6.0</td>
<td>7.11 ± 1.2</td>
<td>14.3 ± 3.4</td>
<td>5.01 ± 1.0</td>
<td>15.5 ± 5.7</td>
</tr>
<tr>
<td>61.7 ± 14.0</td>
<td></td>
<td>62.1 ± 18.7</td>
<td></td>
<td>55.8 ± 20.5</td>
</tr>
<tr>
<td>18.0 ± 4.6</td>
<td>18.4 ± 3.8</td>
<td>15.5 ± 2.9</td>
<td>15.0 ± 5.1</td>
<td>16.8 ± 4.4</td>
</tr>
<tr>
<td><strong>−5.20 ± 26.8</strong></td>
<td></td>
<td><strong>5.10 ± 14.4</strong></td>
<td></td>
<td><strong>5.43 ± 14.2</strong></td>
</tr>
</tbody>
</table>