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ORIGINAL RESEARCH

Sigma-1 receptor concentration in plasma of patients with late-life depression: a preliminary study

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Background: Recently, the sigma-1 receptor has been shown to play a significant role in the neural transmission of mood by regulating N-methyl-D-aspartate receptors. Additionally, the sigma-1 receptor has been reported to influence cognitive functions including learning and memory. In this study, we measured plasma sigma-1 receptor concentrations before and after antidepressant treatment in patients with late-life major depressive disorder (MDD) and explored whether changes in depressive status are related to sigma-1 receptor concentrations.

Methods: The study participants were 12 subjects with late-life MDD diagnosed according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. All of the participants were over 60 years old. Immediately prior to and 8 weeks after the start of treatment, sigma-1 receptor concentration and mental status, including depressive symptoms (Hamilton Depression Rating Scale; HAM-D), were measured. Treatment for depression was performed according to a developed algorithm based on the choice of treatments. We examined the association between changes in sigma-1 receptor concentration and HAM-D scores during antidepressant treatment. For the measurement of plasma sigma-1 receptor concentration, blood plasma samples were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. Western blots were performed using a specific antibody that acts against the sigma-1 receptor, and the net densities of each band were quantified.

Results: All participants showed improvement in depressive symptoms, which was indicated by a significant decrease in the HAM-D scores. The mean plasma sigma-1 receptor concentration also increased significantly following antidepressant treatment. However, no significant correlations were found between changes in plasma sigma-1 receptor concentration and changes in HAM-D scores.

Conclusion: In this preliminary study, we demonstrated that the sigma-1 receptor concentration in plasma increases following antidepressant treatment in patients with late-life MDD. Further studies are warranted to confirm this finding with a larger number of patients.

Keywords: sigma-1 receptor, late-life depression, depressive symptoms, antidepressant treatment

Introduction

Among various biological markers proposed for mood disorders, the recently identified sigma-1 receptor is promising, as it is known to play a significant role in neural transmission of mood by regulating N-methyl-D-aspartate (NMDA) receptors, thereby modulating glutamate activity.[1] The sigma-1 receptor was originally proposed by Martin et al[2] in the 1970s as an opioid receptor subtype. Subsequent pharmacological studies have demonstrated that the sigma-1 receptor is unique and distinct among opioid receptors.[3,12] The sigma-1 receptor, which has a molecular weight of 25 kDa, is a protein

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consisting of 223 amino acids with two transmembrane regions, and it is mainly found in the endoplasmic membrane. In addition to its receptor functions, the sigma-1 receptor has recently been shown to function as a chaperone to stabilize the three-dimensional structure of inositol trisphosphate 3 receptors on the endoplasmic membrane, thereby facilitating intracellular adenosine triphosphate production.[3–13] The sigma-1 receptor exists in a wide range of human tissues from the central nervous system to the peripheral organs, including the brain, liver, sexual glands, kidney, immune organs, and retina.[14]

In the brain, the sigma-1 receptor is specifically distributed in the hippocampus and amygdala, and it plays a particularly important role in neural formation, the induction of differentiation, and in spinal cord formation.[14,15] In addition, the sigma-1 receptor has significant affinity for a wide range of pharmacological agents including antidepressants, antipsychotics, antidementia drugs, antiepileptics, and other psychotrophic drugs.[10,16,17] The physiological functions of the sigma-1 receptor at the cellular level includes regulation of: 1) Ca^{2+} channels in NMDA receptors and endoplasmic membranes; 2) K^{+} channels; 3) free neurotransmitters including dopamine; 4) cellular differentiation; 5) regulation of intracellular lipid distribution; 6) behavioral sensitization to cocaine and amphetamines; and 7) cognitive functions.[14] Studies at the molecular level are ongoing to further elucidate the physiological functions of sigma-1 receptors.

Regarding the pathogenesis of depression, recent neuroimaging studies have demonstrated atrophy of the hippocampus and prefrontal cortices in patients with depression, and postmortem studies have demonstrated neuronal cell loss in the hippocampus in depressed patients, as well as a decrease in the number of glial cells in the prefrontal cortices, implicating these regions as pathognomonic substrates of depression.[18–20] In addition, it has been suggested that antidepressant effects are brought about by neurogenesis or nerve growth factors, including brain-derived neurotrophic factor and insulin-like growth factor-1, and neurogenesis has been proposed as a cellular-level model for recovery from depression.[21]

Decreased sigma-1 receptor activity appears to play a crucial role in the pathophysiology of depression at the level of neurogenesis. In animal studies, sigma-1 receptor knockout mice showed increased immobility in a forced swimming test as a depressive like phenotype, and an agonist of the sigma-1 receptor showed antidepressant effects in animal models, including on the forced swimming test and during a tail-hanging test.[22–26]

Although insight into the relationship between sigma-1 receptors and depression has been gained from investigations in animals, only a limited number of studies have examined the relationship in humans. Takebayashi et al[26] measured the sigma-1 receptor concentration in human plasma and demonstrated that it was decreased in adult male patients with major depressive disorder (MDD) as compared with healthy controls. However, to the best of our knowledge, there have been no human studies that have examined whether the sigma-1 receptor concentration in plasma increases following treatment with antidepressants.

In this study, we measured plasma sigma-1 receptor concentrations before and after treatment in patients with late-life MDD. The main purpose was to determine whether sigma-1 receptor concentrations change as a result of antidepressant treatment. In addition, we explored whether changes in depressive status are related to sigma-1 receptor concentrations. We hypothesized that sigma-1 receptor concentrations would be increased by antidepressant treatment, and that the change in concentration would be correlated with improvements in depressive symptoms.

Methods

Participants

The participants were 12 individuals (ten women and two men) with late-life depression who were either outpatients or hospitalized at Showa University Karasuyama Hospital in Tokyo, Japan, and who were diagnosed with MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision*.[27] All participants were over 60 years old and the mean age was 74.9 (standard deviation [SD] =5.6) years. The mean duration of the newest episode was 13.9 (SD =12.6) months and the mean duration of the illness was 111.2 (SD =184.3) months. The cohort included eight first-episode patients and four patients who had more than two episodes. None of the subjects had been receiving antidepressants at the time of study entry. The subjects were excluded if they had any significant physical illness, neurological illness, history of drug abuse, other comorbidities, or a past history of psychiatric illness, severe cognitive decline on the Mini-Mental State Examination score (score <22),[28] or comorbid personality disorders. All the participants received a head computed tomography scan that demonstrated no significant abnormality. All participants, and their family members when appropriate, gave written informed consent prior to enrollment. The study was approved by the Ethics Committee of Showa University.

Assessment of and treatment for psychiatric symptoms

Immediately prior to and 8 weeks after the start of treatment, mental status examinations – including an assessment of depressive symptoms – were performed. Depressive symptoms were measured using the 17-item Hamilton Depression Rating Scale (HAM-D).[29] Treatment for depression was performed according to an algorithm that was developed in Japan for the treatment of mood disorders, which addressed the choice of antidepressant and nonpharmacological treatment.[30]

Measurement of plasma sigma-1 receptor concentration

The sigma-1 receptor concentration was also measured immediately prior to and 8 weeks after the start of treatment. Blood samples were drawn in ethylenediaminetetraacetic acid-coated Vacutainer® tubes (BD, Franklin Lakes, NJ, USA) and immediately transferred to cryotubes for storage at −80°C prior to being assayed. Each blood sample was diluted 30-fold with ice-cold phosphate-buffered saline and solubilized in sample buffer (100 mM Tris-HCl [pH 6.8], 20% glycerol, 4% sodium dodecyl sulfate [SDS]). The concentration of protein in the samples was standardized by dilution with sample buffer. Total amounts of proteins in each sample were measured by a bicinchoninic acid kit (Pierce Chemical Co, Rockford, IL, USA), and were adjusted to the same amount of 100 μg for all samples. The samples were then treated with 1,4-dithiothreitol and boiled for 5 minutes. Proteins in the samples were separated by SDS–polyacrylamide gel electrophoresis and transblotted to polyvinylidene difluoride membranes. The membranes were blocked with 5% (w/v) skim milk for 6 hours at 4°C, and they were incubated with a specific antibody against guinea pig sigma-1 receptor (a gift from Dr Su, National Institute on Drug Abuse/National Institutes of Health) overnight at 4°C. After washing, the membranes were incubated with horseradish peroxidase-conjugated secondary antibody for 1 hour at room temperature. Chemiluminescent detection was performed using an Immun-Star™ WesternC™ kit (Bio-Rad Laboratories, Hercules, CA, USA), and the net intensities of each band were quantified using the ChemiDoc™ XRS molecular imaging system (Bio-Rad Laboratories).

Data analysis

Analyses were performed using the Statistical Package for the Social Sciences version 17 statistical software (IBM Corporation, Armonk, NY, USA). Changes in sigma-1 receptor concentrations and HAM-D scores prior to treatment and at 8 weeks posttreatment were compared by paired *t*-test. Correlations between changes in sigma-1 receptor concentrations and HAM-D scores were determined using Pearson's correlations.

Results

None of the 12 participants dropped out of the study, and all showed improvement in depressive symptoms. Eight patients received selective serotonin reuptake inhibitors, two received selective serotonin and noradrenaline reuptake inhibitors, and three patients received a noradrenergic and specific serotonergic antidepressant. A total of two patients received multiple antidepressants, and one received an antipsychotic agent. In addition, one patient received modified electroconvulsive therapy. None of the patients showed significant adverse events requiring discontinuation of pharmacotherapy, and none received nonpharmacological treatment aside from ordinary psychotherapy (Table 1).

The mean protein band density for the sigma-1 receptor in plasma samples was 95.6 (range: 26.5–146.2; SD =33.6) before treatment and 111.4 (range: 43.9–178.3; SD =38.6) after 8 weeks of treatment; the difference between pre- and posttreatment was statistically significant (P=0.014).

Changes in the plasma sigma-1 receptor concentration for each participant are shown in Figure 1. Since the number of participants was relatively small, no significant relationship was found between individual drugs and changes in the plasma concentration of the sigma-1 receptor. The sigma-1 receptor concentration in plasma was numerically greater following treatment with each of the medications; however, none of these differences were statistically significant.

Mean HAM-D scores were 29.8 (range: 20–37; SD =5.8) before treatment and 15.3 (range: 5–30; SD =9.3) after treatment, and the difference in depressive symptoms was statistically significant (P<0.001). However, no significant correlations were found between changes in plasma sigma-1 receptor concentrations and changes in HAM-D scores (r=0.092; P=0.775).

Discussion

The present study demonstrated that plasma sigma-1 receptor concentrations increased following antidepressant treatment in patients with late-life MDD. To the best of our knowledge, this is the first study to analyze sequential changes in plasma sigma-1 receptor concentrations in the clinical setting. The results of prior studies in animals suggested the existence of a relationship between

Table 1 Clinical data for and treatment of the individual patients

Patient number	Age (years)	Sex	Duration of the newest episode (months)	Duration of the illness (months)	Medication
1	68	Female	12	12	Fluvoxamine 150 mg
2	77	Male	3	3	Mirtazapine 30 mg Electroconvulsive therapy
3	77	Female	10	10	Paroxetine 40 mg
4	70	Female	10	480	Fluvoxamine 200 mg Sulpiride 100 mg
5	80	Female	20	240	Mirtazapine 45 mg
6	80	Female	14	14	Paroxetine 40 mg
7	81	Female	2	480	Milnacipran 150 mg Sulpiride 150 mg Mirtazapine 30 mg Aripiprazole 6 mg
8	79	Female	14	14	Duloxetine hydrochloride 60 mg
9	81	Male	2	48	Sertraline 75 mg
10	70	Female	24	24	Fluvoxamine 100 mg
11	69	Female	4	4	Sertraline 50 mg
12	67	Female	6	6	Paroxetine 40 mg
Mean (standard deviation)	74.9 (5.6)		13.9 (12.6)	111.2 (184.3)	

sigma-1 receptor and depression.[22] Neurosteroids, including dehydroepiandrosterone, pregnenolone, and progesterone are thought to be potential endogenous ligands because neurosteroids have relatively high affinity for and act as agonists at the sigma-1 receptor.[10] In addition, neurosteroids exhibit an antidepressant effect in the forced swimming test model, and that effect is blocked by NE-100, a specific sigma-1 receptor antagonist. Accordingly, neurosteroids may exert antidepressant effects via the sigma-1 receptor.[25,31] Therefore, our findings may indicate that antidepressant treatments improve depressive symptoms, and that this is accompanied by an increase in the sigma-1 receptor concentration.

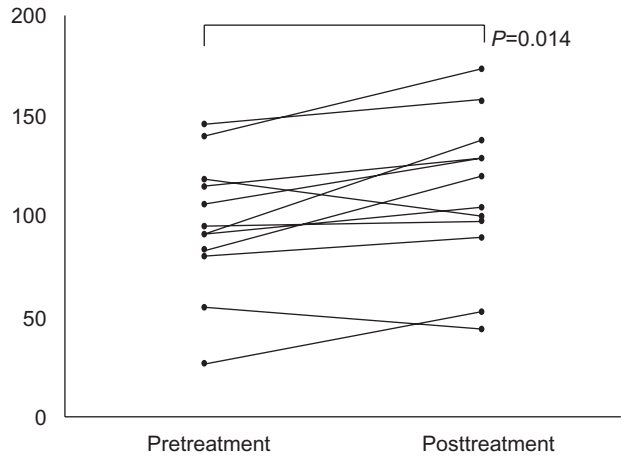

Figure 1 Individual values for plasma sigma-1 concentrations before and after treatment.
Notes: The mean value was 9.7 before treatment and 11.1 after treatment. There was a significant difference between the pre- and posttreatment values.

Although the plasma sigma-1 receptor concentration increased following antidepressant treatment, it did not show a correlation with symptoms of depression. This finding may have been due to the sample size being too small to detect a significant correlation. Further studies with larger sample sizes are needed.

The appropriate sample size for the present study, as determined by statistical power analysis using G*power version 3.1 (Heinrich Heine University, Düsseldorf, Germany) was N=27.[32] Therefore, the present study should be considered as preliminary because the results may lack sufficient statistical power and reliability. In addition, because the study included more females than males, and given that the duration of the last depressive episode and the duration of the illness in males was lower, the results may be biased and not accurately representative of the effect of antidepressants on sigma-1 receptor concentration in depressed patients.

There were several additional limitations in the present study. First, treatment options were not controlled, and no conclusions could be drawn regarding the relationship between individual medications and changes in the sigma-1 receptor concentration. Second, the study examined only patients with depression and did not include a control group of healthy subjects. Previous human studies have revealed that the plasma sigma-1 receptor concentration is lower in patients with MDD than in control subjects.[26] Sigma-1 receptor functioning at baseline in individuals with MDD in the present study was comparable with the results of a previous study.[26]

Third, depressive mood was assessed only by using HAM-D scores. Accordingly, it is not clear whether sigma-1 receptor functions affected depressive mood, concomitant anxiety, or other clinical symptoms. Fourth, the correlation between sigma-1 receptor concentration in plasma and the central nervous system is still unknown. Further studies will be needed to determine the association between sigma-1 receptor concentration in plasma and the central nervous system using another evaluation method, such as positron emission tomography. To address these points, further studies involving more participants, a controlled design, and use of detailed clinical assessment scales is warranted.

In summary, this preliminary study-demonstrated that sigma-1 receptor concentrations are increased following antidepressant treatment in patients with late-life MDD. This is the first study to analyze sequential changes in plasma sigma-1 receptor concentrations in the clinical setting. Further studies are warranted to confirm this finding in a larger cohort of patients.

Disclosure

The authors report no conflicts of interest in this work.

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