Is the GABA System Related to the Social Competence Improvement Effect of Aripiprazole? An 18F-Fluoroflumazenil PET Study

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Objective Patients with schizophrenia who are treated with aripiprazole experience some benefits including an improvement of social competence, but the underlying mechanism of this improvement has not been investigated yet. This study aimed to provide preliminary evidence that the GABA system may be involved in the effect of aripiprazole on social competence.

Methods Seventeen outpatients with schizophrenia (9 taking aripiprazole and 8 taking risperidone) and 18 healthy controls underwent 18F-fluoroflumazenil PET, and GABA_A receptor binding potential was compared between the three groups.

Results Voxelwise one-way ANOVA showed that GABA_A receptor binding potentials in the right medial prefrontal cortex (p=0.04) and right dorsolateral prefrontal cortex (p=0.02) were significantly lower in the aripiprazole group than the risperidone group, and those in the left frontopolar cortex (p=0.03) and right premotor cortex (p=0.02) were significantly lower in the aripiprazole group than the risperidone and control groups.

Conclusion Our results suggest that aripiprazole administration results in increased GABA transmission in the prefrontal regions, and that these increases may be a neural basis of aripiprazole’s clinical benefits on an improvement of social competence.

Key Words GABA_A receptor, Flumazenil PET, Aripiprazole, Social competence, Prefrontal cortex.

INTRODUCTION

Aripiprazole, a relatively new atypical antipsychotic, shares some advantages with other atypical antipsychotics, i.e., effectiveness on both positive and negative symptoms of schizophrenia. Moreover, some studies have shown additional benefits for aripiprazole, despite a controversy about the specificity of the benefits. For example, aripiprazole has a better efficacy in reducing deficit symptoms compared to other antipsychotics such as olanzapine, quetiapine or risperidone.1 Patients who switched from either olanzapine or risperidone to aripiprazole manifested improvements in subjective well-being.2 Our research group demonstrated that the usefulness of aripiprazole in patients with schizophrenia included the improvement of social competence,3 which refers to overall capacity to solve life problems and achieve instrumental and affiliative goals.4 These advantages of aripiprazole may be related to its distinctive pharmacological profile as a partial agonist of D2 and HT1A receptors and as an antagonist of 5-HT2A and 5-HT2C receptors.5 This profile of aripiprazole is contrasted with those of other atypical antipsychotics; for example risperidone acts as a potent antagonist of both 5-HT2 and D2 receptors.6 Although the relationship between aripiprazole and γ-aminobutyric-acid (GABA) is not studied yet, the GABAergic mechanism may be also involved in the advantages of aripiprazole in that GABAergic neurotransmission closely interacts...
with the dopamine and serotonin systems. In fact, dysfunctional GABA transmission in the brain has been considered to play a role in the pathophysiology of schizophrenia. For example, postmortem studies have reported up-regulation of GABA receptor binding in the prefrontal cortex of patients with schizophrenia, whereas in vivo neuroimaging studies using SPECT and $[^{18}C]$Ro15-4513 PET have demonstrated that there is no difference in GABA $\text{A}_$ receptor binding between patients with schizophrenia and healthy controls. Moreover, the GABA system is believed to be related to the mechanism responsible for the efficacy of antipsychotic medications. A previous pharmacomaging study reported that typical and atypical antipsychotics had a different effect on regional GABA activities, but grouped together all atypical antipsychotics in one category and thus ignored a different mechanism of action or efficacy among the drugs. To our knowledge, no studies have examined the difference of regional GABA receptor binding potential between patients taking atypical antipsychotics. Therefore, further study deserves to be performed to clarify the effect on the GABA system by each of atypical antipsychotics including aripiprazole.

It should be considered here that GABAergic inhibition modulates cortical signal transduction operative in information processing. If patients with schizophrenia who administer aripiprazole show a distinctive GABA-related change in some brain regions which are closely related to social functions, it can be considered to be a neural basis of aripiprazole’s additional efficacy, especially on social competence. There are many brain structures that underlie social functions, which includes 1) prefrontal regions including the medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), frontopolar cortex (FPC), and premotor cortex, 2) temporoparietal regions including the temporal pole, superior temporal sulcus, temporoparietal junction and inferior parietal lobule, and 3) the amygdala. Taken together, we regarded these structures as the a priori regions in the present study for investigating changes in GABAergic neurotransmission by aripiprazole.

This study was designed to examine a difference in GABA $\text{A}_$ receptor binding potential between long-term use of aripiprazole and risperidone using $[^{18}F]$-FMZ PET imaging in regions which were related to social functions. We hypothesized that the GABA $\text{A}_$ receptor binding potentials in social competence-related brain regions would be changed in the aripiprazole group.

METHODS

Subjects
Seventeen patients with schizophrenia and 18 healthy controls participated in this study. Inclusion criteria were an exclusive diagnosis of schizophrenia in the patient group and the exclusion of any psychiatric disorder in the control group. Psychiatric diagnoses were assessed with the Structured Clinical Interview for DSM-IV. Clinical symptoms of schizophrenia in the patient group were assessed using the Positive and Negative Syndrome Scale (PANSS). No participants reported any past or present history of significant medical or neurological illness and drug or alcohol abuse. Patients and controls did not significantly differ in gender (eight males in the patient group, nine males in the control group), age (28.7±6.9 years and 26.2±6.9 years, respectively), or years of education (14.0±1.6 years and 13.7±1.5 years, respectively). The study was approved by the institutional review board and written informed consent was obtained from all participants.

The patient group was divided into two subgroups according to antipsychotic medication. Nine patients were taking aripiprazole monotherapy (mean dose: 17.8±9.4 mg) and eight patients were taking risperidone monotherapy (mean dose: 3.4±2.4 mg). All patients and controls had not received benzodiazepines for at least four weeks prior to the PET imaging session, but other medications were not restricted; two patients in the aripiprazole group reported current use of antidepressants, six in the aripiprazole group and one in the risperidone group used propranolol, and six in the aripiprazole group and two in the risperidone group used anticholinergics. There was one left-handed patient in each subgroup. As shown in Table 1, the aripiprazole, risperidone and control groups did not differ in gender, age and years of education. The two medication groups also did not differ in terms of duration of illness, duration of antipsychotics treatment, total and subscale scores of the PANSS, or mean chlorpromazine-equivalent dose of their antipsychotic medication.

$[^{18}F]$-FMZ PET imaging
To investigate GABA $\text{A}_$ receptor binding potential, all subjects were scanned using a GE Discovery STE PET/CT scanner (GE, Milwaukee, WI, USA). A 10 min transmission CT scan was performed for attenuation correction. After injection of approximately 5.5 MBq (0.15 mCi)/kg of $[^{18}F]$-FMZ, a dynamic emission scan was performed in a sequence of 150 frames in 3-D mode (60×10 s, 40×15 s, 20×30 s and 30×60 s) for a total acquisition time of 60 min. As described in our previous study using $[^{18}F]$-FMZ, actual emission data for statistical analysis were obtained for 20 min in 20 min after injection of the radiotracer to avoid blood flow effects and non-specific GABA $\text{A}_$ receptor binding. The attenuation-corrected emission data were reconstructed in a 128×128×47 matrix with a pixel size of 2.34×2.34×3.27 mm using Hanning and Ramp filters.
Table 1. Comparison of clinical and demographic characteristics between the aripiprazole and risperidone groups

<table>
<thead>
<tr>
<th></th>
<th>Aripiprazole group (N=9)</th>
<th>Risperidone group (N=8)</th>
<th>Control group (N=18)</th>
<th>F/T/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.3±5.0</td>
<td>30.1±8.7</td>
<td>26.2±6.9</td>
<td>0.88</td>
<td>0.43</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.9±1.8</td>
<td>14.1±1.6</td>
<td>13.7±1.5</td>
<td>0.25</td>
<td>0.79</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>3/6</td>
<td>5/3</td>
<td>9/9</td>
<td>1.47*</td>
<td>0.48</td>
</tr>
<tr>
<td>Handedness (R/L)</td>
<td>8/1</td>
<td>7/1</td>
<td>18/0</td>
<td>2.26*</td>
<td>0.32</td>
</tr>
<tr>
<td>Dose of antipsychotics</td>
<td>236.9±125.4</td>
<td>168.8±122.3</td>
<td>-</td>
<td>1.13</td>
<td>0.28</td>
</tr>
<tr>
<td>(CP equivalence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)†</td>
<td>4.8±3.0</td>
<td>3.4±1.8</td>
<td>-</td>
<td>1.15</td>
<td>0.27</td>
</tr>
<tr>
<td>Duration of treatment (years)†</td>
<td>1.9±1.0</td>
<td>2.9±1.9</td>
<td>-</td>
<td>-1.30</td>
<td>0.21</td>
</tr>
<tr>
<td>PANSS</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Positive</td>
<td>15.8±4.3</td>
<td>15.6±4.8</td>
<td>-</td>
<td>0.07</td>
<td>0.95</td>
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<tr>
<td>Negative</td>
<td>15.1±3.0</td>
<td>13.5±3.8</td>
<td>-</td>
<td>0.97</td>
<td>0.35</td>
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<tr>
<td>General</td>
<td>29.0±5.5</td>
<td>31.1±6.8</td>
<td>-</td>
<td>-0.71</td>
<td>0.49</td>
</tr>
<tr>
<td>Total</td>
<td>61.0±9.5</td>
<td>60.3±14.1</td>
<td>-</td>
<td>0.13</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Values are presented as means±standard deviation. *Pearson’s chi-square value, †duration of aripiprazole or risperidone was administered. CP: chlorpromazine, PANSS: Positive and Negative Syndrome Scale.
GABA and Aripiprazole

DISCUSSION

A comparison between the patient and control groups revealed that [18F]-FFMZ binding potentials in the medicated patients were increased in the right inferior occipital gyrus, and decreased in the subgenual cingulate cortex and the left temporal pole. Given that increased GABA_A receptor is considered an effect of an upregulation of the GABA_A receptor complex due to presynaptic GABAergic deficiencies, regional increases of GABA_A receptor binding potential may indicate decreased GABA transmission. Therefore, decreased GABA_A receptor binding potential may be interpreted as increased GABA transmission and decreased regional brain activity. Since the subgenual cingulate cortex and the temporal pole has been implicated in emotion regulation, decreased GABA_A receptor binding potential in these regions may be related to emotional abnormality found in patients with schizophrenia. However, given that the patients in this study were medicated

Table 2. Decreased or increased GABA_A receptor binding potential in the patient group when compared with the control group at a threshold of uncorrected p<0.005

<table>
<thead>
<tr>
<th>Regions</th>
<th>Nvox</th>
<th>Zmax</th>
<th>MNI coordinates</th>
<th>Post-hoc</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Decreases in the patient group</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Subgenual cingulate cortex (BA25)</td>
<td>106</td>
<td>2.90</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Left temporal pole (BA38)</td>
<td>23</td>
<td>2.75</td>
<td>-46</td>
<td>18</td>
</tr>
<tr>
<td>Increases in the patient group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right inferior occipital gyrus (BA19)</td>
<td>80</td>
<td>2.76</td>
<td>38</td>
<td>-74</td>
</tr>
</tbody>
</table>

Nvox: number of voxels, Zmax: maximum Z value, MNI: Montreal Neurological Institute, BA: Brodmann area

Table 3. Comparison of GABA_A receptor binding potential among the aripiprazole (A), risperidone (R) and control (C) groups at a threshold of family wise error (FWE) corrected p<0.05

<table>
<thead>
<tr>
<th>Regions</th>
<th>Nvox</th>
<th>Zmax</th>
<th>MNI coordinates</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Right medial prefrontal cortex (BA10)</td>
<td>36</td>
<td>2.52</td>
<td>8</td>
<td>58</td>
</tr>
<tr>
<td>Left frontopolar cortex (BA10)</td>
<td>32</td>
<td>2.52</td>
<td>-22</td>
<td>58</td>
</tr>
<tr>
<td>Right dorsolateral prefrontal cortex (BA46)</td>
<td>29</td>
<td>2.68</td>
<td>36</td>
<td>44</td>
</tr>
<tr>
<td>Right premotor cortex (BA6)</td>
<td>52</td>
<td>2.72</td>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

For post hoc analyses, the whole volumes of the clusters were defined as the regions of interest (ROIs), and the regional mean GABA_A receptor binding potentials of each subject were calculated based on the ROIs using the individual GABA_A receptor binding potential maps. Group comparisons of the ROI values between the aripiprazole and risperidone groups, between the aripiprazole and control groups or between the risperidone and control groups were performed using independent t-tests. Scheffé’s method was applied to correct for multiple comparisons. Significance level for post hoc analyses was set at p<0.05. Nvox: number of voxels, Zmax: maximum Z value, MNI: Montreal Neurological Institute, BA: Brodmann area

Figure 1. GABA_A receptor binding potentials in the right medial prefrontal cortex (MPFC), the left frontopolar cortex (FPC), the right dorsolateral prefrontal cortex (DLPFC) and the premotor cortex (PMC) were significantly lower in the aripiprazole group than the risperidone group [family wise error (FWE) corrected p<0.05].
for a long time, our findings of regional differences of GAB-
Aₐ receptor binding potential might also reflect an effect of
medication or deterioration after long duration of illness.

In a comparison among the three groups, the aripiprazole
group showed significantly decreased [¹⁸F]-FFMZ binding
potentials in the right MPFC, left FPC and right DLPFC com-
pared to the risperidone group, suggesting increased prefrontal
GABA transmission due to aripiprazole. Since appropriate
GABAergic inhibition in the prefrontal cortex is essential for
information processing, increased prefrontal GABA trans-
mission can be interpreted as increased functional activity. The
MPFC is one of the principal components of social brain, brain regions specialized for social cognition. The MPFC in-
tegrates social information across time, allows reflection and
representation of traits and norms, and is also involved in
theory of mind and mentalizing. The FPC acts as a modulator
of social cognition by overriding ongoing processing to
explore new options. In addition, the DLPC is thought to
contribute to cognitive control in social situations by maintain-
ing understanding of one person's intentions and evaluating
whether a second person's actions appear consistent with those
intentions. Collectively, the effect of increased prefrontal
GABA transmission may have possible contribution to aripip-
razole's social competence improvement.

Both the aripiprazole and risperidone groups showed no
significant difference in [¹⁸F]-FFMZ binding potentials in the
right MPFC and right DLPFC compared to the control group.
The functional and structural abnormalities in the MPFC and
DLPFC have been consistently reported in patients with schi-
zophrenia. Moreover, recent studies found elevated GABA
levels in the MPFC in unmedicated patients and altered GABA
receptor subunit in the DLPC in patients regardless of med-
ication use. Comparable levels of GABA, receptor binding
potentials in the MPFC and DLPFC suggest that aripiprazole
and risperidone administration may possibly normalize
GABA alterations in patients with schizophrenia. However,
future studies with drug naïve patients using [¹⁸F]-FFMZ PET
should be warranted because comparable levels of GABA, receptor binding potentials might be due to decreased sensi-
tivity of [¹⁸F]-FFMZ PET imaging.

Compared to both the risperidone and control groups, the
aripiprazole group showed decreased [¹⁸F]-FFMZ binding
potential in the right premotor cortex, which indicates in-
creases in GABA transmission in the premotor area by aripip-
razole. Because GABA inhibits the function of the premotor
cortex, this finding of increased premotor GABA transmission
in the aripiprazole group suggests decreased premotor func-
tioning. The premotor cortex forms the core of the mirror
neuron system which estimates the mental state of the other
person in a social interaction and decreased premotor fun-
ctioning could be opposite of our hypothesis. However, pa-
tients with Parkinson's disease show increased activity in the
premotor cortex compared to healthy controls, and this hy-
peractivation in the premotor cortex decreases after pharma-
cologic treatment. Therefore, decreased premotor function-
ing may be related to less liability for neuroleptic induced
dyskinesia found in aripiprazole compared with risperi-
done. Since social functioning can be negatively influenced
by dyskinesia, decreased premotor activity may be also
possibly linked to social competence improvement by aripip-
razole. But it is hard to interpret that the aripiprazole group
had decreased premotor functioning compared to the con-
trol group. Decreased premotor functioning may be a com-
ensatory mechanism for antipsychotic induced parkinson-
ian symptoms; however, future controlled studies are needed.

The present study has several limitations, most of which stemmed from an open, naturalistic design of the present study in
an outpatient clinic for chronic patients. First, there was a risk of selection bias because the medication groups were not ran-
domly assigned. Second, the sample size of each group was small. Third, the gender ratio in the aripiprazole and risperi-
done groups was not matched. Fourth, measures of social competence, parkinsonian symptoms and smoking history were
not administered. Most of all, we used brain areas instead of
behavioral measures about social competence to explain the
relationship between aripiprazole administration and social
competence improvement. Therefore, future randomized
controlled studies including extensive measures are needed
for more precise conclusions about the relation between me-
dication and behavioral functioning.

In conclusion, administration of aripiprazole resulted in
changes in prefrontal GABA transmission, including in-
creases in the MPFC, FPC, DLPFC and premotor regions. In that
these regions have been reported to be involved in various so-
cial functions, social competence improvement would be one
of the possible reasons for GABA, receptor changes. Despite
limitations, our preliminary study contributes meaningful
data as to how the GABA system may be associated with cli-
nical advantages of aripiprazole.

Acknowledgments

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razole and standard of care in the management of community-treat-
ed schizophrenic patients Schizophrenia Trial of Aripiprazole: (STAR)
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