Dopamine transporter change in drug-naïve schizophrenia: an imaging study with $^{99m}$Tc-TRODAT-1

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Abstract

The aim of this study was to use a specific dopamine transporter (DAT) ligand, $^{99m}$Tc-TRODAT-1 with single photon emission computed tomography (SPECT) to investigate the densities of DAT in the striatal dopaminergic system in patients with schizophrenia.

Striatal DAT uptakes were measured in 12 drug-naïve schizophrenic patients and 12 age- and sex-matched healthy volunteers. The psychometric tools included the Standardized Clinical Assessment for Neuropsychiatry (SCAN) and the Positive and Negative Syndrome Scale (PANSS). Semiquantitative analyses using the ratio of uptake in caudate, putamen, and striatum to occipital lobe, and left–right asymmetry were performed.

Decreased TRODAT uptake in the right striatum and increased uptake in the left striatum were found in the schizophrenics. However, there is no overall difference in the average striatum uptake. The right–left asymmetry of the caudate and putamen DAT binding seen in the healthy control group disappeared in the schizophrenia group. The decreased right uptake and increased left uptake in the striatum might lead to the lack of right–left asymmetry in neuroleptic-naïve schizophrenia patients, confirming that the disorder could be due to a disruption in brain lateralization.

This is the first report on the use TRODAT to evaluate the DAT density in schizophrenia patients and shows lack of asymmetry in striatal uptake of TRODAT in schizophrenics. The findings also suggest that TRODAT SPECT may be a useful technique to measure dopamine transmission in the human brain and for understanding the pathophysiology of neuropsychiatric disorders. © 2003 Elsevier Science B.V. All rights reserved.

Keywords: Dopamine transporter; TRODAT; Schizophrenia

1. Introduction

The dopamine transporter (DAT) is a neuronal element that regulates dopaminergic neurotransmission by terminating the action of dopamine (DA) via reuptake. The density of DAT has been shown to correlate well with the density of dopaminergic nerve terminals (Bannon et al., 1995).

Central dopaminergic hyperactivity has been proposed as a possible etiology of schizophrenia and this hypothesis is complex. Studies measuring dopamine synthesis with [$^{[18]F}$]DOPA and [$^{[1]}C$]DOPA
are also consistent with an increased presynaptic activity in schizophrenia (Reith et al., 1994; Hietala et al., 1995; Hagberg et al., 1998), although this finding has not been replicated in all studies (Dao-Castellana et al., 1997). Recent in vivo imaging studies have provided direct evidence for altered presynaptic dopamine function in neuroleptic-naïve patients with schizophrenia. Presynaptic dopamine synthesis capacity (Hietala et al., 1999), and amphetamine-stimulated dopamine release (Laruelle et al., 1996; Breier et al., 1997) in the striatum are enhanced in patients with schizophrenia.

In addition, the right–left asymmetry of the dopamine synthesis capacity seen in the caudate of young, healthy subjects is lost in neuroleptic-naïve patients with schizophrenia (Hietala et al., 1999; Laakso et al., 2000). Together, these data suggest that an abnormality of dopamine transmission is associated with schizophrenia, and that this abnormality results at least partly from an increase in presynaptic activity (Soares and Innis, 1999). Thus, it is reasonable to consider that there are changes in DAT for patients with schizophrenia.

There have been several post mortem studies on DAT in schizophrenia. Functional DA uptake was reported to be increased in the striatum, whereas the kinetic parameters of the uptake sites were unchanged using different transporter labeling ligands (Pearce et al., 1990; Chingalia et al., 1992; Knable et al., 1994; Laakso et al., 1998). It seems that this marker does not provide any evidence for the dopaminergic hypothesis, but an impairment of the DAT itself could possibly be involved in the etiology of schizophrenia. A defect in DAT, accompanied with increased synaptic DA, may be part of the neuronal abnormality associated with heightened dopaminergic activity in schizophrenia.

The aim of this vivo imaging study was to use single photon emission computed tomography (SPECT) and a specific dopamine transporter ligand, Te-99m TRODAT-1 (TRODAT) (Kung et al., 1996), for investigation of the binding of DAT in the striatal dopaminergic system in first-episode schizophrenic patients, who have never been medicated.

2. Methods

2.1. Subjects

This study was approved by the Institutional Review Boards of Chang-Gung Memorial Hospital. All the patients gave their informed consent.

A total of 12 neuroleptic-naïve patients (10 women and 2 men) who met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV schizophrenia criteria, were diagnosed by board-certified psychiatrists, using the Standardized Clinical Assessment for Neuropsychiatry (SCAN) of the World Health Organization (American Psychiatric Association, 1994; World Health Organization, 1994). Other inclusion criteria were as follows: age between 16 and 45 years old; absence of any previous psychotropic medication; no other DSM-IV axis I diagnosis; no history of alcohol or substance abuse or dependence; no pregnancy; no concomitant or past severe medical conditions; no current suicidal or homicidal ideation; and ability to provide informed consent. All the patients and healthy volunteers were right-handed individuals.

In addition, 12 age-, gender- and race-matched healthy volunteers with no history of mental or physical illness or substance abuse were recruited. They were also interviewed by psychiatrists to rule out any psychiatric disorder. Their mean ages were 25.9 years (S.D. = 7.7) and 29.8 years (S.D. = 8.6), for the patients and controls, respectively. Duration of untreated psychosis was 0.8 ± 1.1 years.

2.2. SPECT procedure

DAT density was measured for all patients and controls, using the radiotracer TRODAT. The drug was prepared by adding Tc-99m pertechnetate to a lyophilized kit from the Institute of Nuclear Energy Research in Taiwan (Kao et al., 2001). Soon after autoclaving and cooling to room temperature, 925 MBq of the drug was injected intravenously. The SPECT images were acquired with a Siemens MultiSPECT 3, triple head gamma camera equipped with fan-bean collimators. The matrix size was 128 × 128. The energy window was set at 140 keV with a 15% symmetric window. SPECT acquisition was performed 4 h after injection of the radiotracer. Images
were acquired with 20 s per projection and 120 projection angles per detector over 360°. Reconstruction of images and attenuation correction were performed as described previously (Kao et al., 2001). Care was taken to minimize misalignment of the patients’ heads, by paying close attention to their positioning during the study and also selecting cooperative individuals.

2.3. Data processing

TRODAT binding in the occipital cortex, total striatum, putamen and caudate nucleus was measured, and the occipital cortex was used as a reference region. A reference magnetic resonance imaging (MRI) brain atlas site by site was used to aid definition of the region of interest (ROI). The DAT density was assessed by manually placing ROIs over three summed reconstructed images with the highest signal in the striatum as the central slice. This is equivalent to coregistering the SPECT scans with a standard MRI image. The specific binding of TRODAT in each of the target regions was calculated as the difference between DAT densities in each of the three target regions (i.e., striatum, putamen and caudate) and the occipital cortex, then divided by the DAT density of the occipital cortex [i.e., (target region DAT density – occipital DAT density)/(occipital DAT density)]. The test–retest variability of radioactivity in healthy volunteers was examined and found acceptable. Test–retest (intra-imaging) variation of reliability did not exceed 5% (3.8 ± 1.6%). Inter-imaging differences were approximately 10% (11.7 ± 3.5%).

2.4. Clinical measures

In patients, the severity of positive and negative symptoms was evaluated with the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). These ratings were obtained at the time of the TRODAT scan, when all patients were free of neuroleptic drugs.

2.5. Statistics

The Mann–Whitney U-test was used to compare variables between the two groups and the Wilcoxon Signed Ranks test was used for right–left comparisons within groups. All tests were two tailed. Relationships between TRODAT binding and symptoms were studied with Pearson’s correlation analysis. P values of less than 0.05 were considered statistically significant.

3. Results

3.1. TRODAT SPECT imaging

The average striatal TRODAT binding potentials were almost identical between the patient and control groups. In the total caudate area, TRODAT binding potential was 1.51 (S.D. = 0.27) in patients and 1.53 (S.D. = 0.29) in controls (Mann–Whitney U-test, \(P = 0.93\)). In the total putamen, TRODAT binding was 1.48 (S.D. = 0.33) in patients and 1.53 (S.D. = 0.25) in controls (Mann–Whitney U-test, \(P = 0.671\)). In the entire striatum, TRODAT binding was 1.48 (S.D. = 0.31) in patients and 1.42 (S.D. = 0.26) in controls (Mann–Whitney U-test, \(P = 0.755\)) (Table 1).

3.2. Symptoms and TRODAT SPECT imaging

In the patient group, PANSS values for positive and negative symptoms of schizophrenia and general psychopathology, did not correlate with the TRODAT binding ratio.

<table>
<thead>
<tr>
<th>Schizophrenia (N = 12)</th>
<th>Controls (N = 12)</th>
<th>Statisticsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean age)</td>
<td>16–42 years old (25.9 ± 7.7)</td>
<td>19–44 years old (29.8 ± 8.6)</td>
</tr>
<tr>
<td>Total caudate</td>
<td>1.51 ± 0.27</td>
<td>1.53 ± 0.29</td>
</tr>
<tr>
<td>Right caudate</td>
<td>1.50 ± 0.30</td>
<td>1.87 ± 0.34</td>
</tr>
<tr>
<td>Left caudate</td>
<td>1.51 ± 0.28</td>
<td>1.20 ± 0.22</td>
</tr>
<tr>
<td>Total putamen</td>
<td>1.48 ± 0.33</td>
<td>1.53 ± 0.25</td>
</tr>
<tr>
<td>Right putamen</td>
<td>1.49 ± 0.33</td>
<td>1.86 ± 0.32</td>
</tr>
<tr>
<td>Left putamen</td>
<td>1.47 ± 0.34</td>
<td>1.21 ± 0.21</td>
</tr>
<tr>
<td>Total striatum</td>
<td>1.48 ± 0.31</td>
<td>1.42 ± 0.26</td>
</tr>
<tr>
<td>Right striatum</td>
<td>1.49 ± 0.33</td>
<td>1.86 ± 0.33</td>
</tr>
<tr>
<td>Left striatum</td>
<td>1.49 ± 0.32</td>
<td>1.21 ± 0.21</td>
</tr>
</tbody>
</table>

N.S. = not significant.

All entries for uptake ratios in this table are presented as mean ± S.D.

a Mann–Whitney U-test.
binding ratio in the entire striatum. These PANSS values were also not significantly correlated with TRODAT binding ratios in the caudate nucleus or putamen.

The duration of untreated psychosis and age of onset of psychotic symptoms were not correlated with specific TRODAT binding ratios. Also, handedness and age apparently had no significant influence on the TRODAT binding ratio.

### 3.3. Higher right side binding in the caudate, putamen, and striatum for normals

In normal subjects, hemisphere laterality in TRODAT binding was noted with greater binding on the right side on the caudate, putamen, and total striatum (Fig. 1). Wilcoxon Signed Rank tests showed statistical significance in the three right–left comparisons (Table 2). In the normals values of the DAT, the binding ratio were $1.87 \pm 0.32$ and $1.20 \pm 0.22$ for the right and left caudates, respectively ($P=0.002$); $1.86 \pm 0.32$ and $1.21 \pm 0.21$ for the right and left putamen, respectively ($P=0.002$); and $1.86 \pm 0.32$ and $1.20 \pm 0.21$ ($P=0.002$) in the right and left striata, respectively.

### 3.4. Lack of asymmetry in the schizophrenia group

In the schizophrenic group, no asymmetry in binding was observed. The values for right and left caudates were $1.50 \pm 0.30$ and $1.51 \pm 0.28$, respectively; for the right and left putamen binding—$1.49 \pm 0.33$ and $1.47 \pm 0.34$, respectively; and for the right and left striata—$1.49 \pm 0.33$ and $1.49 \pm 0.32$, respectively. All values represent the means ± S.D. So an asymmetry of the right and left caudate, putamen and total striatum was observed in the healthy group, but none in the schizophrenia group (Fig. 1). The asymmetry index values ([right − left]/

#### Table 2

The DAT binding ratios on right and left sides of the caudate, putamen, and striatum in both normal and schizophrenic groups and statistical significance, using the Wilcoxon signed rank test

<table>
<thead>
<tr>
<th></th>
<th>Right (mean ± S.D.)</th>
<th>Left (mean ± S.D.)</th>
<th>Statistics²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia group</td>
<td>$1.50 \pm 0.30$</td>
<td>$1.51 \pm 0.28$</td>
<td>N.S.</td>
</tr>
<tr>
<td>Control group</td>
<td>$1.87 \pm 0.32$</td>
<td>$1.20 \pm 0.22$</td>
<td>$P=0.002$</td>
</tr>
<tr>
<td>Putamen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia group</td>
<td>$1.49 \pm 0.33$</td>
<td>$1.47 \pm 0.34$</td>
<td>N.S.</td>
</tr>
<tr>
<td>Control group</td>
<td>$1.86 \pm 0.32$</td>
<td>$1.21 \pm 0.21$</td>
<td>$P=0.002$</td>
</tr>
<tr>
<td>Striatum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia group</td>
<td>$1.49 \pm 0.33$</td>
<td>$1.49 \pm 0.32$</td>
<td>N.S.</td>
</tr>
<tr>
<td>Control group</td>
<td>$1.86 \pm 0.33$</td>
<td>$1.21 \pm 0.21$</td>
<td>$P=0.002$</td>
</tr>
</tbody>
</table>

N.S. = not significant.

All entries for uptake ratios and mean ages in this table are presented as mean ± S.D.

² Wilcoxon signed rank test.
Fig. 2. Asymmetry index of caudate and putamen in normal subjects and patients with schizophrenia.

4. Discussion

4.1. DAT density in drug-naïve schizophrenia

Our results indicate that the average in vivo striatal DAT binding, an index of dopaminergic innervation density, is not altered in neuroleptic-naïve patients with schizophrenia. Our findings are consistent with those of a previous study (Laruelle et al., 2000), which showed no change in striatal DA transporter density in schizophrenia assessed by $^{[123]}$I-CIT SPECT. However, $^{[123]}$I-CIT measures not only the DAT density in the striatum but also the serotonin transporter (SERT) density in the brainstem. In the present study, we report the specific measurements of DAT density in the striatum with SPECT and TRODAT. Although there is no evidence that in humans TRODAT binds to the SERT, there is one report that provides some evidence that it does so in some non-human primates (Dresel et al., 1999). Our findings are supported by several postmortem studies, which showed no change in DA transporter density in schizophrenics (Hirai et al., 1988; Joyce et al., 1988; Czudek and Reynolds, 1989; Pearce et al., 1990; Chingalia et al., 1992; Knable et al., 1994).

Increased presynaptic DA function is a well-known phenomenon in schizophrenia (Hietala et al., 1999; Laruelle et al., 1996, 1999; Breier et al., 1997). Our report indicates that striatal DA hyperactivity in schizophrenia is due to the increased activity rather than to the increased density of dopaminergic terminals in the striatum.

4.2. Lack of correlation between psychopathology severity and TRODAT binding

In the study group, positive and negative symptoms and general psychopathology did not correlate with TRODAT binding ratios in the left and right caudate, putamen, and the entire striatum. Laruelle et al. (2000) reported a “trend level association” or linear association between low striatal DAT density and severity of negative symptoms and they raised the possibility that a relative deficiency in dopamine
terminals in the dorsal striatum may be associated with negative symptoms. Our findings are in line with the report of Lavalaye et al. (2001), in which striatal \([^{123}\text{I}]\) FP-CIT SPECT binding was not significantly different between drug-naïve schizophrenia patients, patients treated with atypical antipsychotics, and normal volunteers. Laakso et al. (2000) also pointed out that the average caudate and putamen DAT binding potentials were almost identical in schizophrenic patients and normals.

No correlation between the duration of untreated psychosis, duration of illness, age and DAT density was demonstrated in our study. Since schizophrenia might be associated with accelerated loss of DAT over the course of the illness (Liberman et al., 1990, 1997), further investigation with larger samples is warranted.

4.3. Lack of right and left asymmetry in the striatum in drug-naïve schizophrenia

Laakso et al. (2000) reported that lateralized DAT density in normal human brains is greater in the right than the left caudate, and no asymmetry was found in the caudates of schizophrenia patients. In the putamen, they found no asymmetry of DAT binding in both patient and control groups. These findings are similar to those observed in an independent study of neuroleptic-naïve patients with schizophrenia who were studied with 6-[\(^{18}\text{F}\)]-fluorodopa (Hietala et al., 1995, 1999). It indicates that both structural and functional impairment of the lateralization of dopaminergic receptors is found in the caudate of patients with schizophrenia.

Our studies support this finding. The normal group showed significant right–left asymmetry of the caudate, putamen, and entire striatum DAT binding, and the schizophrenic group lacked such right–left asymmetry. In the study of Laakso et al. (2000), the schizophrenia patients’ lack of right–left asymmetry was found in the caudate only, while in our study, such lack of asymmetry was evident in both the caudate and putamen, namely in the entire striatum. Although the average striatal DAT density is unaltered in patients with schizophrenia, lack of asymmetry in caudate DAT binding may indicate disrupted brain lateralization in this disorder.

Following a hypothesis of Crow et al. (1989), strong evidence has been provided for decreased cerebral lateralization in schizophrenia (DeLisi, 1995; Sommer et al., 2001). Not only the lack of anatomical asymmetry, but also lateralized brain dysfunction were found in schizophrenic patients (Ragland et al., 1992; Flaum et al., 1995; Goldstein et al., 1999; Soares and Innis, 1999). So psychotic disorders may be due to developmental anomalies of cerebral asymmetry. Our functional imaging study supports this hypothesis.

4.4. Limitations of the present study

To avoid tilt and misalignment of the patient’s head in the scanner, we chose cooperative patients and carefully positioned and monitored them during the scans to reduce movement artefacts. This possible important limitation is also noted in other brain imaging studies on drug-naïve psychotic subjects. Although “noise” could be added to the data from movement of the patient’s head, this is unlikely to add a left–right bias. The second limitation is lack of the formal MRI co-registration of the SPECT procedures. But a reference magnetic resonance imaging brain atlas site by site was used to define the ROIs, as is mentioned above, and there was a coregistration of SPECT with a standard MRI.

4.5. TRODAT as a specific DAT binding tool in future neuropsychiatric imaging studies

Our findings indicate that TRODAT brain SPECT is an appropriate method for evaluating the DAT density in human brains. But the complex nature of the dopaminergic hypothesis of schizophrenia also allows for increased activity. Several studies have also pointed out TRODAT’s specificity in evaluating DAT in various neuropsychiatric disorders, for example, Parkinson’s disease, attention deficit hyperactivity disorder, etc. (Tzen et al., 2001; Kao et al., 2001; Dresel et al., 2000; Mozley et al., 2000). These findings suggest that SPECT is a useful technique to measure DA transmission in human brains and it may further our understanding of the pathophysiology of neuropsychiatric disorders. The range of such disorders can be extended and, to our knowledge, this is the first report to use TRODAT in evaluating the DAT density in schizophrenic patients.
5. Conclusions

The present study supports the hypothesis of dysregulation of the striatal presynaptic DA system in patients with schizophrenia and indicates the following:

1. Average striatal DAT binding is unchanged in neuroleptic-naïve patients with first-episode schizophrenia, which suggests that the previously reported dysregulation in striatal presynaptic DA function in patients with schizophrenia is not due to an altered number of dopaminergic terminals.

2. The asymmetry in DAT binding in the caudate, putamen, and the entire striatum, found in normals is absent in patients with schizophrenia. This phenomenon is probably part of a larger disturbance of structural and functional brain asymmetry in such patients.

3. No relationship was observed between TRODAT binding and the clinical measures studied.

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References


