Dopamine transporter density in schizophrenic subjects with and without tardive dyskinesia

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Abstract

Striatal dopamine transporter (DAT) binding potential (BP) was compared between schizophrenic subjects with and without tardive dyskinesia and controls. Although the groups were not statistically different in striatal BP, tardive subjects had apparently lower DAT density than non-tardive schizophrenic subjects. Significant and trend-level inverse correlations were found between DAT BP in the striatum, and especially the severity of negative symptom scores, but also cognitive, and depression/anxiety scores on the PANSS.

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1. Introduction

Tardive dyskinesia (TD) is a serious oral-facial movement disorder that is often linked to chronic treatment with typical antipsychotics, although the exact causality remains unexplained. Animal studies suggest that a compromised nigrostriatal dopaminergic projection may be involved in development of abnormal oral movements after chronic treatment with typical neuroleptics (Gunne et al., 1982; Huang and Kostrzewa, 1994; Huang et al., 1997). We sought to compare striatal dopamine transporter (DAT, a marker for dopamine terminals) levels in schizophrenic subjects with and without TD. Although a recent SPECT study (Lavalaye et al., 2001a) found no differences in dopamine terminals) levels in schizophrenic subjects with and without TD. Although a recent SPECT study (Lavalaye et al., 2001a) found no differences in DAT density between controls and patients with TD, to date there has been no direct comparison between schizophrenic subjects with and without TD. However, lower amounts of DAT relative to control subjects have been reported in subjects with chronic schizophrenia (Laakso et al., 2001), which is a population at increased risk for TD. It was hypothesized that sub-
jects with TD would have lower striatal DAT levels compared to schizophrenic subjects without tardive dyskinesia (NTD).

A second component of this study investigated the relationship between DAT density and symptom severity in schizophrenia. A trend-level negative correlation was observed between striatal DAT density and negative symptoms (Laruelle et al., 2000). Another study reported a positive correlation between L-DOPA uptake in the right putamen and degree of paranoid symptoms and a negative correlation between left striatal L-DOPA uptake and depressive symptoms (Hietala et al., 1999). Other studies have found no association between DAT and symptom scores (Laakso et al., 2000, 2001; Lavalaye et al., 2001a). It should be noted that these studies utilized different imaging methodologies and different subscales of PANSS. In accordance with the dopamine hypothesis of schizophrenia, it was predicted that DAT density would have a positive relationship with the severity of positive symptoms, with the inverse relationship occurring between DAT levels and negative symptoms.

2. Subjects and methods

Ten schizophrenic (eight males, two females) and ten control (seven males, three females) subjects completed this study after receiving an explanation of the procedures and signing an informed consent statement approved by the Indiana University Institutional Review Board. Subjects met DSM-IV criteria for schizophrenia and had no Axis II diagnoses. Diagnoses were made by experienced psychologists using the structured clinical diagnosis schedule for DSM-IV (SCID-IV). Schizophrenic subjects taking neuroleptic medication had been diagnosed previously as NTD or TD subjects during a drug wash-out period in the preceding 3 months for another study. Subjects were classified as NTD if they presented with a score below minimal on the “global severity of abnormal movements” item on the Abnormal Involuntary Movement Scale. For ethical reasons, neuroleptic medications were allowed during this study; typical and atypical antipsychotics are unlikely to interfere with DAT binding (Allard et al., 1990; Scheffel et al., 1996; Reader et al., 1998). One subject (NTD) was medication naïve, three subjects (one NTD, two TD) were taking atypical neuroleptics, five subjects (three NTD, two TD) were receiving typical neuroleptics, and one subject (TD) had a history of typical neuroleptic medication and had been drug-free for one month.

PANSS interviews were conducted in 7 of the 10 schizophrenic subjects (4 NTD, 3 TD) by qualified clinicians. Scores were calculated using the standard PANSS, stratified as a five-factor model (Lindenmayer et al., 1994, 1995) with the following symptom domains: positive, negative, cognitive, excitement, and depression/anxiety.

PET scans with $[^{11}	ext{C}]$CFT were conducted for 90 min either on a Siemens ECAT 951R or an EXACT HR+ scanner (CTI, Knoxville, TN) as previously described (Brashear et al., 1999). MR images were not available for all subjects; as such, regions of interest (ROIs) were placed directly on late-time average PET images for uniformity of data collection. Circular ROIs were placed on both hemispheres. The ROI volumes were: caudate, 656.2 mm$^3$, putamen, 525.0 mm$^3$, cerebellum, 262.5 mm$^3$. Time activity cures were generated in MEDx, and exported to a Matlab (Mathworks, Natick, MA) implementation of the Logan plot with a reference region (cerebellum) as an input function (Logan et al., 1996) to estimate the parameter of interest, binding potential ($BP = \frac{DVR}{C0} - 1$). Logan plots were linear.

One-way ANOVA was used to test age and binding potential between control, NTD, and TD. Student’s t-test was used to test BP between controls and combined schizophrenic subjects ($n = 10$). Pearson’s correlation analysis was used to examine relationships between BP and PANSS subscale scores, and between BP and age. Statistical significance was set at $p < 0.05$. Trend-level was defined as $0.05 < p < 0.1$. Data are Mean ± S.D. unless otherwise specified.

3. Results

Subject groups were not significantly different from one another in age ($p = 0.45$). Ages were: controls, $45.0 ± 18.3$ years; NTD, $35.0 ± 7.78$; TD, $46.0 ± 13.9$.

There were no statistical differences in BP between groups in any region. Compared to the NTD group, DAT BP of TD subjects was 26.9% and 24.2% lower.
in the left and right caudate, respectively. Similar differences were found in the left (26.7%) and right (24.8%) putamen (Fig. 1).

BP data from the NTD and TD groups were combined, and compared to control values with t-tests. There were no differences in DAT BP for any region between the combined schizophrenic group and controls (data not shown).

Table 1 shows the results from the correlational analyses between DAT BP and age, by group. Age was significantly negatively correlated with DAT BP in all regions in control subjects, and in the right caudate in TD subjects.

Table 1
Pearson’s r values for age and DAT BP by region and group

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Left caudate</th>
<th>Right caudate</th>
<th>Left putamen</th>
<th>Right putamen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>−0.91*</td>
<td>−0.86*</td>
<td>−0.70*</td>
<td>−0.745*</td>
</tr>
<tr>
<td>NTD</td>
<td>5</td>
<td>0.46</td>
<td>0.75</td>
<td>0.64</td>
<td>0.72</td>
</tr>
<tr>
<td>TD</td>
<td>5</td>
<td>−0.03</td>
<td>−0.92*</td>
<td>−0.12</td>
<td>−0.11</td>
</tr>
<tr>
<td>NTD + TD</td>
<td>10</td>
<td>−0.15</td>
<td>−0.35</td>
<td>−0.12</td>
<td>−0.09</td>
</tr>
</tbody>
</table>

* p < 0.05.

Table 2
Pearson’s r values for PANSS subscale scores and DAT BP by region (n = 7)

<table>
<thead>
<tr>
<th>PANSS subscale</th>
<th>Left caudate</th>
<th>Right caudate</th>
<th>Left putamen</th>
<th>Right putamen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>−0.20</td>
<td>0.39</td>
<td>−0.02</td>
<td>0.17</td>
</tr>
<tr>
<td>Negative</td>
<td>−0.76**</td>
<td>−0.61</td>
<td>−0.79**</td>
<td>−0.87*</td>
</tr>
<tr>
<td>Excitement</td>
<td>−0.43</td>
<td>0.07</td>
<td>−0.27</td>
<td>−0.05</td>
</tr>
<tr>
<td>Cognitive</td>
<td>−0.79**</td>
<td>−0.35</td>
<td>−0.67*</td>
<td>−0.61</td>
</tr>
<tr>
<td>Depression/Anxiety</td>
<td>−0.66*</td>
<td>−0.45</td>
<td>−0.69*</td>
<td>−0.47</td>
</tr>
</tbody>
</table>

* 0.05 < p < 0.1.
** p < 0.05.
Table 2 contains the results of the correlation analyses between DAT BP and PANSS subscale scores. There were statistically significant and trend-level inverse correlations between DAT BP and negative, cognitive, and depression/anxiety symptom domains, especially in the left striatum. No significant relationships were detected between positive or excitement PANSS scores and DAT BP in any region.

4. Discussion

Our results suggest that there are no overt differences in striatal DAT density between control, NTD, and TD subjects. This is in agreement with other reports that have used similar radioligands for examining DAT in schizophrenia (Laakso et al., 2000; Laruelle et al., 2000; Lavayle et al., 2001b). However, the TD group showed a consistently lower DAT BP in all regions compared to the NTD group. As the TD group is older than NTD group, it is possible that this is related to age-related declines in DAT (e.g., 8% per decade, van Dyck et al., 1995; 6.6% per decade, Volkow et al., 1996); however, this would not account for the ~26% decrease in DAT BP. There was also no relationship between DAT BP and age in any schizophrenic group (except for right caudate, TD). This suggests that the lower DAT BP in TD subjects may be caused by a phenomenon other than age-related decline. Further studies are needed to compare dopaminergic markers between schizophrenic subjects with and without TD.

This study also examined the relationships between DAT density and symptom severity in schizophrenia. Significant inverse correlations between DAT BP and negative, cognitive, and depression/anxiety scores were found. This suggests that decrements in dopamine signaling may play an important part in the severity of these syndrome domains in schizophrenia. Although this study is small, we found no support for the hypothesized relationship between DAT BP and positive symptom ratings in schizophrenic subjects. Although positive symptoms such as hallucinations and delusions are thought to result from a hyperdopaminergic state, the striatum may not be the anatomical location of overactive dopaminergic neurons contributing to hallucinations and delusions in schizophrenia. In addition, it should be considered that five of these seven patients were on low-dose medication, which possibly obscured detection of any relationship between DAT density and positive symptom scores. Alternatively, the amount of striatal dopamine innervation may not be directly related to positive symptoms. Studies conducted with medication-naïve or medication-withdrawn patients are needed to further explore this question, in addition to examination of limbic and temporal cortical dopamine systems with respect to schizophrenic symptomatology.

In conclusion, the present study provides preliminary evidence to support an inverse relationship between the severity of negative, cognitive, and depression/anxiety symptoms in schizophrenia and the amount of striatal dopamine innervation. Further PET studies examining this relationship are needed to confirm the data presented here.

Acknowledgements

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References


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