Low Dopamine D₂ Receptor Binding in Subregions of the Thalamus in Schizophrenia

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Objective: Several structural and functional brain imaging studies have pointed to a disturbance of thalamic subnuclei in patients with schizophrenia. The dopamine hypothesis of schizophrenia has, however, not been thoroughly examined in terms of this complex structure, which has connections with most brain regions of central interest in schizophrenia research. The aim of the present study was to examine dopamine D₂ receptor binding in subregions of the thalamus in patients with schizophrenia.

Method: The authors used positron emission tomography and the radioligand [¹¹C]FLB457 to examine dopamine D₂ receptor binding in thalamic subregions of 10 drug-naive patients with schizophrenia. Binding potential was calculated by the reference tissue method and used as an index for dopamine D₂ receptor binding. Comparisons were made with 19 healthy subjects. Subregions of interest were defined on individual magnetic resonance images using a percentage-based operational approach. Clinical symptoms were rated by using the Brief Psychiatric Rating Scale (BPRS).

Results: The [¹¹C]FLB457 binding potential was lower in the central medial and posterior subregions of the thalamus in patients with schizophrenia. At a functional level, there was a significant negative correlation between binding potential and BPRS positive symptom scores.

Conclusions: The subregions with low D₂ receptor binding comprise primarily the dorsomedial nucleus and pulvinar, two important components in circuitries previously suggested in the pathophysiology of schizophrenia. Aberrant dopaminergic neurotransmission in thalamic subregions might be a mechanism underlying positive symptoms in schizophrenia.

The dopamine D₂ receptor has long been of central interest in research on the pathophysiology of schizophrenia. Early positron emission tomography (PET) studies focused on the striatum, a region with a high density of D₂ receptors. Improvements in PET methodology now allow the examination of low-density dopamine D₂ receptor populations in several limbic and cortical regions in which structural or biochemical abnormalities have been reported in schizophrenia. In a recent analysis of cortical and subcortical regions, we found low radioligand binding to dopamine D₂ receptors in the anterior cingulate cortex of patients with schizophrenia and a correlation with positive symptom scores (1). On the other hand, functional abnormality of schizophrenia has also been discussed in terms of thalamic circuitry (2). Imaging studies have consistently revealed smaller thalamic volumes in patients with schizophrenia as well as altered thalamic perfusion and metabolism (2–13). Neuropathological studies have found a reduction in the number of neurons in the mediodorsal nucleus of the thalamus in schizophrenia brains (14–17). Schizophrenia-associated neuronal loss has also been found in the pulvinar (17). A synapse-related protein study reported that the thalamic abnormalities include synaptic disturbances (18).

The thalamus was not included in early maps showing dopaminergic innervation in the rodent brain (19). However, dopamine D₂ receptors have more recently been identified in the human thalamus in vitro (20, 21) and in vivo using PET (22–24). The possibility that dopamine D₂ receptors in the thalamus are involved in the therapeutic actions of antipsychotics has been supported by PET studies that demonstrated dopamine D₂ receptor occupancy in the thalamus by antipsychotic drugs (25). Each of the major 23 subnuclei of the thalamus (26) has a unique set of efferent and afferent projections with different functional implications. In a previous study, we found a tendency toward low density of dopamine D₂ receptors in the thalamus (1). However, in that study we focused on the thalamus as a whole and did not take its detailed complexity into account.

The aim of the present PET study was to examine separately dopamine D₂ receptor binding in five major subregions of the thalamus. Ten neuroleptic-naive patients with schizophrenia and 19 healthy comparison subjects were examined with the radioligand [¹¹C]FLB457, a substituted benzamide with a very high affinity for dopamine D₂ re-

between patients (mean=2.6, SD=0.7) and comparison subjects (mean=7.5). Parental socioeconomic status was determined on the basis of the interplane septa retracted. A bolus of 89.5–249.0 MBq (mean=172.5, SD=40.0) of $^{11}$C]FLB457 with high specific radioactivity (64.9–534.9 GBq/μmol) was injected intravenously into a cannula inserted in an antecubital vein. The cannula was then flushed by the rapid injection of 20 ml of saline. Radioactivity in the brain was measured in a series of scans for 80 minutes starting immediately after the injection. The emission scans were reconstructed with a Hanning filter cutoff frequency of 0.4 (full width at half maximum=7.5 mm). Images from the reconstructed volume were displayed as 67 horizontal sections. MR images were acquired on a Phillips Gyroscan NT, 1.5 tesla. $T_1$-weighted images of the brain were obtained to allow for differentiation between white and gray matter. The scan parameters for 1-mm-thick, three-dimensional $T_1$ images in the transversal plane were as follows: TR/TE=19/10 msec, flip angle=30°, matrix=256×256, field of view=256×256 mm, number of excitations=1.

### Quantitative Analysis of $[{^{11}}C]$FLB457 Binding

Quantitative analysis was performed using the three-parameter simplified reference tissue model (30, 31). The cerebellum was used as a reference region because it has been shown to be almost devoid of $D_2$ receptors (23, 31). The model provides an estimation of the binding potential, which is defined by the following equation:

$$BP = \frac{k_3}{k_4} = \frac{B_{max}}{K_d \left[ 1 + \sum \frac{F_i}{K_{di}} \right]}$$

where $k_3$ and $k_4$ describe the bidirectional exchange of tracer between the free compartment and the compartment representing specific binding, $f_2$ is the “free fraction” of nonspecifically bound radioligand in brain, $B_{max}$ is the receptor density, $K_d$ is the equilibrium dissociation constant for the radioligand (32), and $F_i$ and $K_{di}$ are the free concentration and the dissociation constant of competing endogenous dopamine, respectively. The model also provides the parameter $R_1$, which represents the ratio of radioligand delivery in the region of interest to that in the reference region (influx ratio).

### Thalamic Subdivisions

Regions of interest for five operationally defined subregions of the thalamus were defined on MR images according to a manual tracing technique that has been described in the literature. The thalamus was subdivided into five distinct regions. The thalamus was first divided into medial and lateral parts. A line drawn parallel to the lateral border of the midbrain, the interhemispheric fissure, and the cerebral aqueduct represented the vertical bisection (coronal view in Figure 1). This line was continued through all thalamic slices to create a plane of bisection parallel to the interhemispheric fissure. The individual number of contiguous coronal slices in which the thalamus appeared was then calculated.

The thalamus was divided into anterior, central, and posterior divisions that were defined as fixed percentages of the total number of coronal slices. The anterior and central divisions each contained 40% of the total number of slices, and the posterior division contained 20%. Using this approach, the thalamus was divided into six subregions. The medial and lateral portions of the posterior thalamus were then combined, since they both corresponded to the pulvinar (axial view in Figure 1). In the final step, the regions of interest were linearly transformed using the parameters obtained from the coregistration of the individual MRI and PET images. This was done using SPM 99 (34), with the default parameter option of mutual information (35). After transformation of the regions of interest from MRI to PET, the regional radioactivity of each region of interest was calculated for each frame, corrected for decay, and plotted against time. The average values for

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regions of interest in the right and left hemisphere were used to increase the signal-to-noise ratio for the calculations. Subdivision of the thalamus and measurement of binding potential values was performed in duplicate by a single investigator (F.Y.) in 10 of the healthy subjects, and intrarater reliability was assessed. High intraclass correlations (ICCs) for subregions were seen for the two sets of measurements (anterior medial: ICC=0.96, anterior lateral: ICC=0.94, central medial: ICC=0.92, central lateral: ICC=0.90, posterior: ICC=0.82).

Morphological analysis was performed on the volume of the region of interest defined on MRI images. The size of the area was calculated, summed across slices, and multiplied by the slice thickness (1 mm), yielding approximate volumes. Intracranial volume was used as a covariate when comparing volumetric measures between the groups.

**Statistical Comparisons**

The binding potential and influx ratio (RI) values for the whole thalamus were compared between patients and healthy subjects by Student’s t test. The volumes for the whole thalamus were compared between patients and comparison subjects using one-way analysis of covariance (ANCOVA) with the intracranial volume as covariate. Group differences in the binding potential values of the thalamic subregions were compared by using multivariate analysis of variance (MANOVA). Follow-up serial one-way analyses of variance (ANOVA) were performed to specify regional differences. To examine the influence of regional differences of blood flow and volumes on those of the binding potential values, serial one-way ANOVAs and ANCOVAs with intracranial volume as covariate were performed to specify regional differences of the influx ratios and volumes, respectively. A p value of 0.05 (two-tailed) was chosen as the significance threshold. The relationship between regional binding potential values and BPRS scores (total score as well as positive and negative symptom subscale scores) was evaluated in the correlation analysis. In consideration of the effect of the duration of illness, we examined the relationship of its variables to regional binding potential values. We also evaluated the relationships of age and parental socioeconomic status to the binding potential values in healthy subjects and patients. In the correlation analysis, we used the Pearson correlation method, and p<0.01 [0.05/5] was considered as significant to avoid type I errors due to the multiplicity of statistical analyses.
TABLE 1. [11C]FLB457 Binding Potential in Thalamic Subregions of Patients With Schizophrenia and Healthy Comparison Subjects

<table>
<thead>
<tr>
<th>Thalamic Subregion</th>
<th>Healthy Subjects (N=19)</th>
<th>Schizophrenia Patients (N=10)</th>
<th>Analysis of Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Anterior medial</td>
<td>3.72</td>
<td>0.70</td>
<td>3.67</td>
</tr>
<tr>
<td>Anterior lateral</td>
<td>2.69</td>
<td>0.51</td>
<td>2.55</td>
</tr>
<tr>
<td>Central medial</td>
<td>3.95</td>
<td>0.48</td>
<td>3.53</td>
</tr>
<tr>
<td>Central lateral</td>
<td>2.56</td>
<td>0.38</td>
<td>2.43</td>
</tr>
<tr>
<td>Posterior</td>
<td>2.64</td>
<td>0.26</td>
<td>2.33</td>
</tr>
</tbody>
</table>

*Index of dopamine D2 receptor binding.

With regard to the binding potential values for [11C]FLB457 binding in the whole thalamus, there was no significant difference between the two groups (schizophrenia patients: mean=3.31, SD=0.33; comparison subjects: mean=3.54, SD=0.45) (t=1.45, df=27, p>0.15). However, multivariate analyses of the binding potential values in the thalamic subregions showed significant differences between patients with schizophrenia and comparison subjects. Follow-up ANOVAs revealed that the binding potential values in the central medial region and the posterior region were significantly lower in the patients (Table 1, Figure 2).

The influx ratio (R1) for the whole thalamus (schizophrenia patients: mean=0.84, SD=0.50; comparison subjects: mean=0.87, SD=0.57) did not differ significantly between patients and comparison subjects (t=1.62, df=27, p>0.12) nor did it differ in any subregion (Table 2). The volume of the whole thalamus was not significantly different between patients (mean=8.65, SD=1.16) and healthy subjects (mean=8.65, SD=1.19) (F=0.005, df=1, 26, p=0.94), and no significant difference was found for any of the thalamic subregions (Table 2).

For the central medial region and the posterior region there was a statistically significant negative correlation between binding potential and positive symptom subscores on the BPRS (Table 3, Figure 3). There was no significant correlation between binding potential and the BPRS total scores or negative symptom subscore for any region. Further, no significant relationship was observed between regional binding potential values and the duration of illness, age, or parental socioeconomic status in comparison subjects and patients.

Discussion

In a previous PET study, we reported low dopamine D2 receptor binding in the anterior cingulate in patients with schizophrenia and a statistical trend for low binding in the thalamus (1). In the present study with a partly overlap-
agonist apomorphine into the medial thalamus (43). The dorsomedial nucleus has connections to the prefrontal cortex and anterior cingulate (44). Both these regions have also been included in discussions on the gating function (39). An abnormality of the dorsomedial nucleus in schizophrenia may be attributed to functional disturbances in any of the brain regions discussed in relation to sensory gating.

The other subnuclei with low binding potential are found in the pulvinar. This is one of several structures implicated in attentional processing and salience (45–47). The pulvinar has connections with the visual and auditory cortex as well as the prefrontal cortex and temporal association areas (48). A primary abnormality in the pulvinar may thus induce unusual associations and sensory disturbances in schizophrenia (26). Taken together, these two regions may have a functional role consistent with several of the disturbed functions in schizophrenia and underlie the correlation with BPRS positive symptom score.

The observation of a significant negative correlation between subregional binding potential and positive symptom score is similar to that previously reported for $[^{11}C]$FLB457 binding in the anterior cingulate. The anterior cingulate has direct connections with the dorsomedial nucleus and the pulvinar (48–50). When we examined the relationship between dopamine D$_2$ receptor binding in the central medial and posterior regions of the thalamus and that of the anterior cingulate using the Pearson correlation method, we found a significant interrelationship between those regions in patients with schizophrenia (p<0.05). The abnormality shown in the thalamic subregions might have a similar background to that in the anterior cingulate. However, the cellular localization of D$_2$ receptors in the thalamic subregions that might allow speculation about the altered regulatory function of interneurons with D$_2$ receptors has not yet been determined, as discussed in the previous study (1).

Reduced regional blood flow has been reported in the thalamus of schizophrenia (51). However, the reduction of binding potential is unlikely to be a result of altered blood flow, since the R$_1$ value did not differ significantly between the healthy subjects and patients. While morphological changes have been reported in the thalamic mediodorsal nucleus and pulvinar in schizophrenia (7, 8), and this can affect binding potential, no significant difference was observed in the volumes of thalamic subdivisions, including the central medial and posterior regions, between our examined patient and comparison groups. The relatively moderate severity and short duration of illness in our pa-

<table>
<thead>
<tr>
<th>Thalamic Subregion</th>
<th>Influx Ratio$^a$</th>
<th>Analysis of Variance</th>
<th>Volume (cm$^3$)</th>
<th>Analysis of Covariance$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy Subjects (N=19)</td>
<td>Schizophrenia Patients (N=10)</td>
<td></td>
<td>Healthy Subjects (N=19)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Anterior medial</td>
<td>0.87</td>
<td>0.06</td>
<td>0.83</td>
<td>0.07</td>
</tr>
<tr>
<td>Anterior lateral</td>
<td>0.80</td>
<td>0.08</td>
<td>0.77</td>
<td>0.08</td>
</tr>
<tr>
<td>Central medial</td>
<td>0.92</td>
<td>0.08</td>
<td>0.88</td>
<td>0.04</td>
</tr>
<tr>
<td>Central lateral</td>
<td>0.90</td>
<td>0.06</td>
<td>0.87</td>
<td>0.06</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.80</td>
<td>0.06</td>
<td>0.78</td>
<td>0.05</td>
</tr>
</tbody>
</table>

$^a$ The ratio of radioligand delivery in the region of interest to that in the reference region (cerebellum).

$^b$ Intracranial volume entered as covariate.

<table>
<thead>
<tr>
<th>Thalamic Subregion</th>
<th>Total Scale</th>
<th>Positive Symptoms</th>
<th>Negative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>Anterior medial</td>
<td>-0.06</td>
<td>0.86</td>
<td>-0.18</td>
</tr>
<tr>
<td>Anterior lateral</td>
<td>0.06</td>
<td>0.88</td>
<td>0.39</td>
</tr>
<tr>
<td>Central medial</td>
<td>-0.04</td>
<td>0.05</td>
<td>-0.78</td>
</tr>
<tr>
<td>Central lateral</td>
<td>-0.03</td>
<td>0.03</td>
<td>-0.11</td>
</tr>
<tr>
<td>Posterior</td>
<td>-0.58</td>
<td>0.08</td>
<td>-0.80</td>
</tr>
</tbody>
</table>

$^a$ Index of dopamine D$_2$ receptor binding.
tient group may explain the lack of volume change (52, 53). In any case, low dopamine D2 receptor binding can therefore not be attributed to reductions in gross brain anatomy.

There are several confounding factors in this study. First, the number of patients was small, raising the question of adequate statistical power, and thus it cannot be ruled out that a larger study population might reveal that the binding potential values of other thalamic subregions and volumetric measurements will also show significant differences. In addition, [11C]FLB457 has high affinity not only for dopamine D2 receptors but also for dopamine D3 receptors (27). Dopamine D3 receptors are distributed mainly to the ventral striatum and the islands of Calleja in the postmortem human brain, but they have as yet not been distinctly identified in the thalamus (54–56). Thus, there is a possibility that our findings could be partly explained by the reduction of dopamine D3 receptors, but this will have to await the outcome of future studies on the amount of dopamine D3 receptors in the thalamus. Another factor is that psychopathology was assessed by the 18-item BPRS, but this scale mainly measures the affective component of the negative symptoms and does not cover well the additional components that identify cognitive, anergic, and social dimensions (57).

Finally, our measurement of thalamic subdivisions has several limitations. We were unable to delineate and employ an intrathalamic marker as a consistent landmark for our regional subdivisions. Rather, we relied upon approximate percentage-based divisions of the total thalamic area as a means of dividing the thalamus. This automated method reduced some of the subjectivity and systematic bias involved in defining subthalamic areas with limited resolution imaging. However, without manual editing, the assumptions that all thalamic nuclei are consistently represented by these rigid subdivisions cannot be assured, and the volume of each subdivision would not be comparable with data from carefully edited volumetric studies.

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