Decreased thalamic D₂/D₃ receptor binding in drug-naive patients with schizophrenia: a PET study with [¹¹C]FLB 457

Mirjam Talvik, Anna-Lena Nordström, Hans Olsson, Christer Halldin and Lars Farde

Department of Clinical Neuroscience, Psychiatry Section, Karolinska Psychiatric Centre, Karolinska Hospital, S-171 76 Stockholm, Sweden

Abstract

The thalamus is a neuroanatomic structure that has reciprocal connections with several brain regions suggested to be involved in the pathophysiology of schizophrenia. Recent studies have reported structural as well as functional abnormalities of the thalamus in schizophrenia. The aim of the present exploratory study was to examine D₂/D₃ dopamine receptors in the thalamus as well as the anterior cingulate and the frontal and temporal cortices by using the high-affinity radioligand [¹¹C]FLB 457 and positron emission tomography (3D PET) and to explore the data in relation to disease, age and psychopathology. Nine drug-naive patients with schizophrenia and eight control subjects were examined. Regional binding potential (BP) values were calculated using the simplified reference tissue model. The D₂/D₃ receptor binding was significantly lower in the right medial thalamus in the schizophrenia patients compared to control subjects. In addition, we found a significant negative age effect on the D₂/D₃ BP in the frontal and temporal cortex for both groups. There was no significant age effect on the D₂/D₃ BP in the thalamus or in the anterior cingulate. The result provides additional support to the view that the age effect on D₂/D₃ receptors differ between brain regions. The preliminary finding of low thalamic D₂/D₃ BP in patients strengthens the hypothesis that the thalamus is a key region in the pathophysiology of schizophrenia.

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Key words: Age, anterior cingulate, dopamine, frontal cortex, PANSS, temporal cortex.

Introduction

Several brain regions such as the basal ganglia, limbic structures and neocortical regions have been implicated in the pathophysiology of schizophrenia (Alzheimer, 1897; Andreasen et al., 1986; Csernansky et al., 1991; Goldman-Rakic et al., 1992; Heckers et al., 1991; Weinberger et al., 1992a). Of these regions, the thalamus is a neuroanatomic structure of particular interest since it is involved in neurocircuits suggested to be important in the pathophysiology of schizophrenia (Young et al., 1991). Findings of thalamic abnormality in schizophrenia at a functional level as well as at a structural level has provided increasing support for this view (Andreasen et al., 1994; Buchsbaum et al., 1996; Danos et al., 1998).

The dopamine hypothesis for schizophrenia states that the symptoms are related to an overactivity in central dopaminergic neurotransmission (Van Rossum, 1967). The hypothesis has been examined in positron emission tomography (PET) studies by examination of radioligand binding to dopamine D₂ receptors in patients, in vivo. Most of the studies have failed to replicate the initial post-mortem findings of elevated D₂ receptors in schizophrenia (Farde et al., 1987, 1990; Hietala et al., 1994; Martinot et al., 1990; Nordström et al., 1995; Owen et al., 1978; Tune et al., 1993; Wong et al., 1986). However, these studies have focused on the striatum, a large region with dense dopaminergic innervation, thus providing a suitable signal for quantification using the first generation of PET systems.

The development of high resolution three-dimensional (3D) PET and high-affinity radioligands has made it possible to examine not only the striatum but also regions with low D₂ receptor densities, such as the thalamus and the neocortex (Farde et al., 1997;
The first PET study of extrastriatal D\textsubscript{2} receptor binding in drug-naive patients with schizophrenia, has recently been published (Suhara et al. 2002). Low D\textsubscript{2} receptor binding was demonstrated in the anterior cingulate in 11 drug-naive patients with schizophrenia compared to controls. In addition, the authors reported a significant negative correlation between the D\textsubscript{2} binding potential (BP) in the anterior cingulate and positive symptoms.

The first aim of the present PET study was to use the high-affinity radioligand [\textsuperscript{11}C]FLB 457 to examine D\textsubscript{2}/D\textsubscript{3} receptor binding in the thalamus, the anterior cingulate and the frontal and medial temporal cortex in drug-naive patients with schizophrenia and control subjects. A second aim was to examine the effect of age on D\textsubscript{2}/D\textsubscript{3} binding in the extrastriatal regions. A third aim was to search for relationships with the D\textsubscript{2}/D\textsubscript{3} receptor binding to psychopathology as assessed with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987).

Subjects and methods
The research project was approved by the Ethical and Radiation Safety Committees at the Karolinska Hospital and was conducted according to the Declaration of Madrid. All subjects gave oral and written informed consent.

Control subjects
Eight control subjects, four men and four women; mean age 31 yr (S.D. 12 yr) were included. They were healthy according to physical examination, psychiatric interview, blood and urine analysis and MRI of the brain. They had no history of psychiatric illness or head injury. They had not taken any CNS drugs and were medication free at the time of assessment.

Patients
Fourteen patients with schizophrenia, according to DSM-IV criteria were consecutively recruited from the Karolinska Psychiatry Centre in Stockholm. Two patients were withdrawn before the PET examination due to severe deterioration. Three patients initially approached, chose not to participate in the PET examination. Nine patients, 3 men and 6 women mean age 36 yr (S.D. 12 yr) completed the study according to the protocol. All patients were drug-naive concerning neuroleptic medication. Exclusion criteria were psychiatric comorbidity, history of head injury, drug addiction or ongoing pregnancy/lactation.

Clinical assessment
The patients were diagnosed by a research psychiatrist (M.T.) using the Structured Clinical Interview for DSM-IV. The symptoms were rated according to the PANSS, including categorization for the positive, negative and general subscales (Kay et al., 1987). Drug screening was performed using urine sampling. Concomitant medication with benzodiazepines (oxazepam 10–25 mg single oral dose) was allowed as anxiolysis during the PET examination.

Preparatory activities and MRI
A head-fixation system with an individual plaster helmet was used both in the PET and MRI measurements to allow the same head positioning in the two imaging modalities (Bergström et al., 1981; Farde et al., 1989). To obtain anatomical correlates, a MRI scan was performed for each individual. A MR Advantage System, 1.5-T GE Signa was used in a fast spin-echo sequence with a moderately T\textsubscript{2}-weighted protocol.

PET experimental procedure
The radioligand [\textsuperscript{11}C]FLB 457 with picomolar affinity for D\textsubscript{2}/D\textsubscript{3} receptors was used for the PET examination (Halldin et al., 1995). The radioligand was injected into the right antecubital vein for 2 s and the cannula was then immediately flushed with 10 ml saline. The mean injected radioactivity was 241 MBq (s.d. 30 MBq) and the specific radioactivity ranged between 81.4 and 210.9 Ci/mmol at time of injection. The PET system in use was Siemens ECAT EXACT 47, run in 3D mode. The axial resolution was 3.8 mm and the resolution in plane was 4 mm full-width half maximum (FWHM) (Wienhard et al., 1994). Brain radioactivity was measured for 51–63 min. The reconstructed data were displayed as 47 horizontal sections with a centre-to-centre distance of 3.125 mm.

Image analysis
Regions of interest (ROI) were delineated on the MR images and transferred to the PET images. By inspection of the image circumference the ROIs could be moved to adjust for errors of positioning in plane (Farde et al., 1989). ROIs were defined for the thalamus, the anterior cingulate and the frontal and temporal cortices, i.e. regions formerly suggested in the pathophysiology of schizophrenia (Alzheimer, 1897; Andreasen, 1997; Benes, 1993; Füngfeld, 1954; Mullan and Penfield, 1959; Pakkenberg, 1990; Suhara et al., 2002; Weinberger et al., 1992b). The ROIs for the
temporal cortex include superior, medial and inferior gyri. Two ROIs were drawn for the thalamus that was thereby hemisectioned from the anterior pole to the mid of the pulvinar nuclei. The division allowed differentiation between limbic/cortical (the medial thalamus, i.e. the anterior nucleus, the mediodorsal and the central nuclei) and motor-related (the lateral thalamus, i.e. mainly ventral posterior nucleus) regions in the thalamus (Kiernan, 1998). All target ROIs were drawn on three sections above the first appearance of the superior collicle. In addition ROIs for the cerebellum were defined on three sections beneath the first appearance of the petrosal bone (Talvik et al., 2001). Data from the series of sections were pooled to obtain the average radioactivity concentration of the whole volume of interest and were plotted vs. time (Olsson et al., 1999).

\[ ^{11} \text{C} \]FLB 457 binding potential (BP) in the ROIs was calculated using the simplified reference tissue model (Lammertsma and Hume, 1996). In addition to the BP the model also provides \( R_1 \), a parameter that reflects the rate of radioligand delivery to the ROI. The cerebellar cortex, a region with negligible levels of \( D_2 \) receptors was used as the reference region (Hall et al., 1996a).

Statistics

Group and side differences in BP were tested with repeated measures ANOVA (hemisphere x diagnosis). The association between the BP and age within groups as well as the difference between groups was also tested with linear regression to allow estimation of the size of the age effect. Positive group results were tested with two-tailed \( t \) tests. Results with significantly different variances were further tested with two-tailed \( t \) tests for unequal variances. The associations between BP and ROI volume as well as BP and \( R_1 \) was tested with linear regression analysis in a similar way. Correlations between BP and PANSS was analysed using the Spearman rank-correlation coefficient. We chose not to make correction for multiple comparisons in order to avoid a type II error in this preliminary study.

Results

Eight control subjects and nine drug-naive patients with schizophrenia were examined according to the protocol (Table 1). The groups were similar with respect to age and gender. The injected mass of radioligand was similar for both groups [mean 0.86 \( \mu \text{g} \) (S.D. 0.22 \( \mu \text{g} \)) and 0.82 \( \mu \text{g} \) (S.D. 0.42 \( \mu \text{g} \)) for control subjects and patients respectively]. There was a significant age effect on the \( D_2/D_3 \) BP of \(-0.01 \times \text{year} \) in the frontal and temporal cortex \((p<0.05)\). In the thalamus and in the anterior cingulate, there was no significant age effect on the \( D_2/D_3 \) BP.

When tested with repeated measures ANOVA (hemisphere as dependent variable, group as independent variable, age as covariate) there were no significant side or group differences in \( D_2/D_3 \) BP in the anterior cingulate, the frontal cortex, the temporal cortex or the lateral thalamus. In the medial thalamus there was no significant group effect \([F(1,14)=1.45, \ p=0.25]\) however, there was a significant group x hemisphere interaction \([F(1,14)=10.7, \ p=0.006]\) (Table 3). To further investigate this interaction, both hemispheres were subsequently tested with \( t \) tests. There was a significant difference in \( D_2/D_3 \) BP between patients and control subjects in the right medial thalamus \((p=0.043)\). This \( t \) test was done with separate variance estimates due to a significant difference in

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Subtype of schizophrenia</th>
<th>Duration of illness (yr)</th>
<th>PANSS score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>Paranoid</td>
<td>&gt;5</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Paranoid</td>
<td>&gt;1</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Paranoid</td>
<td>&gt;5</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Paranoid</td>
<td>&gt;4</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Paranoid</td>
<td>&lt;1</td>
<td>124</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Paranoid</td>
<td>&gt;1</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Paranoid</td>
<td>&gt;5</td>
<td>57</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>Paranoid</td>
<td>&gt;1</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>Paranoid</td>
<td>&gt;2</td>
<td>112</td>
</tr>
</tbody>
</table>

Table 1. Patient characteristics
Table 2. The ROI volume and ratio of delivery (R₁) in all regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Control (n = 8) Mean (s.d.)</th>
<th>Patient (n = 9) Mean (s.d.)</th>
<th>R₁ Control (n = 8) Mean (s.d.)</th>
<th>Patient (n = 9) Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right medial thalamus</td>
<td>2067 (182)</td>
<td>2086 (202)</td>
<td>0.99 (0.08)</td>
<td>0.88 (0.12)</td>
</tr>
<tr>
<td>Left medial thalamus</td>
<td>2133 (146)</td>
<td>2058 (179)</td>
<td>0.98 (0.09)</td>
<td>0.95 (0.12)</td>
</tr>
<tr>
<td>Right lateral thalamus</td>
<td>1883 (124)</td>
<td>1847 (164)</td>
<td>0.98 (0.08)</td>
<td>0.95 (0.08)</td>
</tr>
<tr>
<td>Left lateral thalamus</td>
<td>2448 (154)</td>
<td>2267 (234)</td>
<td>0.93 (0.07)</td>
<td>0.94 (0.09)</td>
</tr>
<tr>
<td>Right anterior cingulate</td>
<td>791 (220)</td>
<td>771 (279)</td>
<td>0.76 (0.08)</td>
<td>0.84 (0.12)</td>
</tr>
<tr>
<td>Left anterior cingulate</td>
<td>870 (150)</td>
<td>810 (441)</td>
<td>0.74 (0.07)</td>
<td>0.79 (0.10)</td>
</tr>
<tr>
<td>Right frontal cortex</td>
<td>7449 (738)</td>
<td>7038 (883)</td>
<td>0.87 (0.07)</td>
<td>0.89 (0.09)</td>
</tr>
<tr>
<td>Left frontal cortex</td>
<td>7203 (716)</td>
<td>7027 (1207)</td>
<td>0.88 (0.07)</td>
<td>0.88 (0.09)</td>
</tr>
<tr>
<td>Right temporal cortex</td>
<td>10385 (1275)</td>
<td>9613 (1624)</td>
<td>0.93 (0.09)</td>
<td>0.92 (0.07)</td>
</tr>
<tr>
<td>Left temporal cortex</td>
<td>9494 (759)</td>
<td>8659 (1505)</td>
<td>0.93 (0.06)</td>
<td>0.88 (0.10)</td>
</tr>
</tbody>
</table>

Table 3. The D₂/D₃ BP as measured with PET and [¹²C]FLB 457

<table>
<thead>
<tr>
<th>Region</th>
<th>Control (n = 8) Mean (s.d.)</th>
<th>Patient (n = 9) Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right medial thalamus</td>
<td>4.06 (1.05)</td>
<td>3.13 (0.33)</td>
</tr>
<tr>
<td>Left medial thalamus</td>
<td>3.49 (0.57)</td>
<td>3.63 (0.75)</td>
</tr>
<tr>
<td>Right lateral thalamus</td>
<td>2.96 (0.67)</td>
<td>2.78 (0.56)</td>
</tr>
<tr>
<td>Left lateral thalamus</td>
<td>2.40 (0.44)</td>
<td>2.94 (1.19)</td>
</tr>
<tr>
<td>Right anterior cingulate</td>
<td>0.92 (0.50)</td>
<td>1.17 (0.56)</td>
</tr>
<tr>
<td>Left anterior cingulate</td>
<td>0.80 (0.47)</td>
<td>1.09 (0.59)</td>
</tr>
<tr>
<td>Right frontal cortex</td>
<td>0.67 (0.30)</td>
<td>0.70 (0.24)</td>
</tr>
<tr>
<td>Left frontal cortex</td>
<td>0.67 (0.31)</td>
<td>0.64 (0.18)</td>
</tr>
<tr>
<td>Right temporal cortex</td>
<td>1.07 (0.39)</td>
<td>1.26 (0.32)</td>
</tr>
<tr>
<td>Left temporal cortex</td>
<td>1.13 (0.40)</td>
<td>1.08 (0.25)</td>
</tr>
</tbody>
</table>

a BP in patients < BP in control subjects, p < 0.05 analysed with two-tailed t test for separated variance estimate.
b Age-dependent decrease of BP, p < 0.05 tested with linear regression analysis.
c The difference in D₂/D₃ BP between patients and control subjects in the right medial thalamus is significantly different from the D₂/D₃ BP between patients and control subjects in the left medial thalamus (significant interaction term) [F(1,14) = 10.7, p = 0.006].

variances between the groups (p = 0.004). The positive result was further confirmed with a non-parametric test (Mann–Whitney; exact p = 0.027). In the left medial thalamus there was no significant difference in D₂/D₃ BP between patients and control subjects (p = 0.67).

The groups did not differ with respect to ROI volumes or R₁ (Table 2). There was no significant association in patients and control subjects between D₂/D₃ BP and ROI volume or D₂/D₃ BP and R₁ respectively. For the cerebellum the mean Area Under the Curve for the radioactivity over time (AUCₚₑₚ) was 1062 (s.d. 228) for control subjects and 1134 (s.d. 148) for patients respectively with no significant group difference (two-tailed t test, p = 0.4).

Total PANSS score ranged between 57 and 124 (Table 1). The score for the positive, negative and general subscales ranged between 21–29, 9–43 and 20–56 respectively. There was no significant correlation between total PANSS, positive, negative or general PANSS subscales and D₂/D₃ BP in the right medial thalamus. There was a significant correlation between general psychopathology, assessed with PANSS and D₂/D₃ BP in the right lateral thalamus using Spearman rank-correlation coefficient (r = 0.8, p = 0.01). There were no significant correlations between general PANSS and D₂/D₃ BP in other regions, nor between total PANSS, positive or negative PANSS and D₂/D₃ BP (Table 4).

Discussion

In the present study we examined the D₂/D₃ binding in a series of regions implicated in the pathophysiology of schizophrenia. We found no significant differences in the D₂/D₃ BP in the anterior cingulate, the frontal cortex or the temporal cortex between patients and control subjects. However, we found a significantly lower D₂ binding in the right medial thalamus in patients with schizophrenia compared to control subjects. Suhara et al. (2002) has recently reported a significant decrease in the D₂ receptor BP in the anterior cingulate. We were not able to replicate this finding. However, both the present study and the
study by Suhara et al. (2002) include limited samples of patients, which may contribute to the discrepant results. Interestingly though, a tendency towards lower BP in the thalamus in schizophrenia patients was also indicated in the Suhara et al. study. The anterior cingulate and the medial thalamus are both part of the same pathway and taken together these results point to a possible pathological process in a common functional circuitry.

Early post-mortem studies have reported cell loss in the thalamus of patients with schizophrenia (Fu¨nfgeld, 1954). The findings have been supported in more recent studies of the mediodorsal thalamus (Pakkenberg, 1990, 1992). In addition, reduced densities of thalamocortical projection neurons in the anterioventral nucleus as well as volume and neuronal changes in the right mediodorsal and pulvinar nuclei in schizophrenia subjects has been reported (Byne et al., 2002; Danos et al., 1998). In studies in vivo, smaller thalamic volumes on the right side have been reported in an MRI study on patients with schizophrenia (Andreasen et al., 1994). The finding has been independently confirmed by other groups (Gilbert et al., 2001; Staal et al., 1998). Interestingly, thalamic abnormalities in schizophrenia have also been reported in functional studies using different approaches (Buchsbaum et al., 1996, 2002; Danos et al., 2001). Taken together, studies using different methods on distinct thalamic parameters, converge on pathology of the right thalamus in schizophrenia (Andreasen et al., 1994; Buchsbaum et al., 1996; Byne et al., 2002; Danos et al., 1998). Hemispheric imbalance, an explanatory model for psychiatric illness since the 19th century, has gained increased interest during the last decades (Cummings, 1997; Lohr and Caligiuri, 1997). With particular regard to the schizophrenia syndrome is that right-side pathology may affect the communicative value of the language, specific aspects of perception as well as the sphere of thinking (Cutting, 1992).

It has been hypothesized that the aetiology of schizophrenia is related to a defect in brain circuitries involving the thalamus (Andreasen, 1997; Jones, 1997; Weinberger, 1997). The hypothesis is based on the observations that the thalamus has reciprocal projections with regions associated with limbic, motor and sensory function. The physiological role of the thalamus may thus explain the diverse perceptual, emotional and cognitive symptoms in schizophrenia (Young et al., 1991). In earlier studies, the thalamus has not been considered in relation to the dopamine hypothesis of schizophrenia. It was not until recently that autoradiographic studies revealed the existence of relatively high densities of D₂-like receptors in the human thalamus (Hall et al., 1996a; Kessler et al., 1993). A role of the thalamus in relation to the dopamine hypothesis has been corroborated by recent findings of the thalamus as a potential site of anti-psychotic drug action (Deutch et al., 1995; Mukherjee et al., 2001; Nyberg et al., 2002; Talvik et al., 2001; Xiberas et al., 2001b). The lower thalamic D₂/D₃ BP found in the present study converge with previous findings of a disturbed dopaminergic transmission in the thalamus in schizophrenia.

**Table 4.** The D₂/D₃ BP correlated to PANSS

<table>
<thead>
<tr>
<th>Region</th>
<th>Total</th>
<th>Positive</th>
<th>Negative</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Right medial thalamus</td>
<td>−0.20</td>
<td>0.61</td>
<td>−0.24</td>
<td>0.52</td>
</tr>
<tr>
<td>Left medial thalamus</td>
<td>−0.53</td>
<td>0.14</td>
<td>−0.24</td>
<td>0.54</td>
</tr>
<tr>
<td>Right lateral thalamus</td>
<td>−0.63</td>
<td>0.08</td>
<td>0.20</td>
<td>0.60</td>
</tr>
<tr>
<td>Left lateral thalamus</td>
<td>−0.05</td>
<td>0.90</td>
<td>0.08</td>
<td>0.84</td>
</tr>
<tr>
<td>Right anterior cingulate</td>
<td>−0.23</td>
<td>0.55</td>
<td>−0.15</td>
<td>0.69</td>
</tr>
<tr>
<td>Left anterior cingulate</td>
<td>−0.06</td>
<td>0.55</td>
<td>−0.20</td>
<td>0.60</td>
</tr>
<tr>
<td>Right frontal cortex</td>
<td>−0.07</td>
<td>0.86</td>
<td>−0.26</td>
<td>0.49</td>
</tr>
<tr>
<td>Left frontal cortex</td>
<td>0.02</td>
<td>0.97</td>
<td>−0.42</td>
<td>0.26</td>
</tr>
<tr>
<td>Right temporal cortex</td>
<td>0.30</td>
<td>0.43</td>
<td>−0.33</td>
<td>0.38</td>
</tr>
<tr>
<td>Left temporal cortex</td>
<td>0.03</td>
<td>0.93</td>
<td>0.04</td>
<td>0.91</td>
</tr>
</tbody>
</table>

a General PANSS score was significantly correlated to the D₂/D₃ BP in the right lateral thalamus.
BP is the ratio between $D_2/D_3$ receptor density and apparent affinity. The concept of apparent affinity includes the affinity of the radioligand to the receptor and also an effect of the concentration of endogenous dopamine (Mintun et al., 1984; Olsson et al., 1999). Thus, the finding of a lower $D_2/D_3$ BP in the right medial thalamus can represent low receptor density or be a result of altered dopamine levels in the thalamus. Findings of decreased cell count and synaptic loss in the thalamus of schizophrenia patients supports the interpretation that low $D_2/D_3$ represents an actual reduction of receptor density (Bennow et al., 2000; Pakkenberg, 1990). However, it cannot be excluded that the decreased BP may be caused by regional differences in dopamine concentrations in patients. For the striatum, altered levels of dopamine in patients with schizophrenia has been shown in both challenge studies and in studies of baseline dopamine levels (Abi-Dargham et al., 1998, 2000; Breier et al., 1997; Laruelle et al., 1996). The present finding of low thalamic $D_2/D_3$ BP awaits the development of refined methodology to evaluate the effect of dopamine challenges in regions with low $D_2/D_3$ receptor expression (Chou et al., 2000; Okauchi et al., 2001).

Using PET and $[11^C]$FLB 457 it has been shown that an age-related loss of $D_2$ receptors also occurs in extrastriatal regions (Inoue et al., 2001; Kaasinen et al., 2000). Several PET studies have indicated an age-dependent decline of the $D_2$ receptors in the striatum (Antonini et al., 1993; Martinot et al., 1991; Nordström et al., 1992; Pohjalainen et al., 1998; Rinne et al., 1993).

In the present study there was a significant negative age effect on the $D_2/D_3$ BP in the frontal and the temporal cortices. This is consistent with the two earlier studies demonstrating an age-related loss of $D_2$ receptors in the extrastriatal region of approx. 10% per decade. We found no significant age effect in the thalamus or in the anterior cingulate. It is noteworthy that both Kaasinen et al. (2000) and Inoue et al. (2001) found a lower $D_2$ receptor decrease rate per age in the thalamus compared to the cortical regions (5–6% per decade). The result from the present study provides additional support for the view that the age effect on $D_2$ receptors differs between brain regions.

In mRNA studies, $D_2$ and $D_3$ receptors have been shown to be widely expressed in the human brain, although differently distributed (Hurd et al., 2001; Suzuki et al., 1998). Autoradiographic studies have indicated the presence of low levels of both $D_2$ and $D_3$ receptors in human neocortex (Hall et al., 1996a,b). The thalamus shows higher concentrations of the $D_2$ and $D_3$ receptors with an equal distribution in anteroventral and mediodorsal nuclei (Gurevich and Joyce, 1999). It has been suggested that $D_2$ receptor sensitization in limbic regions may underlie the development of psychosis (Flores et al., 1996; Richtand et al., 2001). However, post-mortem studies of $D_3$ receptor density in patients with schizophrenia have yielded discrepant results (Gurevich et al., 1997; Meador-Woodruff et al., 1997). The lack of suitable ligands with high selectivity for the $D_3$ receptor has limited the research and in-vivo studies of the interaction between the two receptor types are not available. FLB 457 has a high affinity for $D_2$ as well as $D_3$ receptors (Halldin et al., 1995). The finding of lower BP in the right medial thalamus could thus reflect group differences in $D_3$ as well as $D_3$ receptors.

BP was analysed using the simplified reference region model suitable for low-receptor-density regions (Lammertsma and Hume, 1996). The $D_2$ binding received with the high-affinity radioligand $[11^C]$FLB 457 has been shown to have good test–retest reliability in extrastriatal regions (Sudo et al., 2001; Vilkman et al., 2000). The cerebellum, a region practically devoid of $D_2$ receptors, is commonly used as a reference region (Hall et al., 1996a). However, even the existence of minute concentrations of receptors in the reference region may provide a signal with a high-affinity radioligand. Kinetic analyses of FLB 457 binding in the cerebellum have yielded somewhat discrepant results with regard to the existence of significant specific binding in the region (Delforge et al., 2001; Olsson et al., 1999; Suhara et al., 1999, 2002; Xiberas et al., 2001a). It is thus possible that the BP in the regions examined in the present study is to some extent underestimated. In addition, group differences in cerebellar-specific binding could cause apparent group differences in the ROIs. However, there was no statistical group difference in the AUC_{cer}, i.e. an estimate of the radioactivity in the cerebellum. The finding of group differences in thalamic BP should thus not depend on the choice of cerebellum as the reference region.

The occupancy induced by a high-affinity radioligand depends on the specific activity of the injected substance. High specific activity would result in low injected mass and low occupancy. The specific activity in the present study is within the range of previously published studies with $[11^C]$FLB 457 (Sudo et al., 2001; Suhara et al., 1999, 2002; Vilkman et al., 2000). In addition, the specific activity and injected mass did not differ significantly between the groups. Another methodological issue is that patients with schizophrenia may have alterations in regional cerebral blood flow (Buchsbaum et al., 1996; Heckers et al.,
2000; McGuire et al., 1993; Weinberger et al., 1992b). However, the reduction in BP is unlikely to be an effect of altered blood flow, since the ratio of delivery (RI value) did not differ between the groups. Structural studies have indicated that the thalamus is smaller in patients, which would result in smaller ROI volumes in patients than in control subjects. Smaller ROI volumes in patients could falsely result in a too low BP, due to partial volume effects. However, the ROI volumes did not differ between groups.

The $D_2/D_3$ BP in the right medial thalamus did not correlate to total PANSS or to any of the three subscales in this study on a small sample of drug-naive patients. There was however, a correlation between general PANSS and the $D_2/D_3$ BP in the right lateral thalamus. Previous studies with different methods give limited support to pathology in the lateral thalamus and in the present study there was no biochemical deviation in this region. It is questionable if the correlation to general psychopathology in this study is of importance or represents random significance in this sample of nine patients.

In this study of nine drug-naive patients with schizophrenia and eight control subjects we found an age-related decrease of $D_2/D_3$ BP in the cortex. The age effect was in the same range as previously reported and did not differ between the groups. Consistent with observations of thalamic abnormality in schizophrenia we found a lower $D_2/D_3$ BP in the right medial thalamus in patients compared to controls. The hypothesis of the thalamus as a key region in the pathophysiology of schizophrenia builds upon a series of converging observations using different methods. Taken together, our preliminary finding of low $D_2/D_3$ BP in the thalamus indicates aberrant dopaminergic function in the thalamo-cortical circuitry.

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