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ORIGINAL PAPER

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Midbrain dopamine $D_{2/3}$ receptor binding in schizophrenia

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Abstract Several studies suggest that dysregulation of dopaminergic transmission in the midbrain and thalamus may contribute to the symptomatology of schizophrenia. The objective of this study was to examine the putative alteration of dopamine $D_{2/3}$ receptor densities in the thalamus and midbrain of drug-naïve schizophrenic patients. We used the high-affinity single-photon emission tomography ligand [^{123}I]epidepride for imaging $D_{2/3}$ receptor binding sites in six neuroleptic-naïve schizophrenic patients, and seven healthy controls. Schizophrenic symptoms were evaluated by the Positive and Negative Syndrome Scale. Significantly lower $D_{2/3}$ values were observed in the midbrain of patients with schizophrenia compared to controls ($P = 0.02$). No statistically significant difference was observed in the thalamus between two groups. Negative correlations were found between thalamic $D_{2/3}$ receptor binding and general psychopathological schizophrenic symptoms (r from −0.78 to −0.92). These observations implicate altered dopaminergic activity in the midbrain of schizophrenic patients.

Key words dopamine · epidepride · schizophrenia · substantia nigra · thalamus

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Introduction

According to pharmacological evidence, dopaminergic neurotransmission plays an important role in the pathophysiology of schizophrenia [1, 2]. It has been proposed that schizophrenia is characterized by abnormally low mesocortical dopamine activity, which causes cognitive deficits and negative symptoms, and by elevated dopamine transmission in subcortical regions, which is associated with positive symptoms [3, 4]. The results from transmitter-specific ligands indicate that a subgroup of schizophrenic patients may have elevated D_2 binding in the basal ganglia [5, 6], and some in vivo neuroimaging studies have shown elevated striatal presynaptic dopamine turnover in the acute phase of unmedicated schizophrenics [7, 8]. A recent theory for the pathogenesis of schizophrenia suggests that there may be a decrease in tonic dopamine release, which eventually results in an abnormally high phasic release of dopamine in the striatum of schizophrenic patients [3, 9]. In the human brain, the highest D_2 receptor density has been observed in the striatum, which receives dopaminergic projections from the substantia nigra, where a moderate amount of D_2 receptors are found [10, 11]. It has been suggested that these nigral D_2 receptors serve as autoreceptors that regulate nigrostriatal dopamine function [11, 12].

Several studies have repeatedly demonstrated both structural and functional alterations in extrastriatal

regions in schizophrenia, mostly in the prefrontal cortex and the temporal lobe (e.g., 13–15]. These regions connect to the thalamus, which modulates multiple neuronal interconnections that may be dysfunctional in schizophrenia [16]. Thalamic volume reduction and cell loss in the nuclei, which communicate with the prefrontal cortex and limbic regions, have been documented in in vivo neuroimaging and postmortem studies on drug-naïve schizophrenic patients [17, 18]. In addition, recent functional studies have revealed a correlation among schizophrenic patients between thalamic abnormalities and both cognitive and psychotic symptoms [19, 20, 21]. The significance of dopamine transmission in the thalamus has been demonstrated in a recent immunocytochemical study with primates, which suggests that dopamine may contribute the cognitive processes via projections from the prefrontal cortex to the thalamic termination field [22]. Also, a recently published in vivo study on extrastriatal D_2 binding in neuroleptic-naïve schizophrenic patients using positron emission tomography (PET) indicated significantly decreased D_2 receptor binding values in the right thalamus compared to controls [23]. The result was replicated in some subregions of the thalamus showing also negative correlation between dopamine $D_{2/3}$ receptor densities and positive symptoms of schizophrenia [24]. However, nothing is known about possible abnormalities in the dopamine D_2 receptor levels in the midbrain of living schizophrenic patients.

Previously, we reported extremely low $D_{2/3}$ receptor binding among drug-naïve schizophrenic patients in both hemispheres of the temporal cortex, compared with controls, in addition to strong negative correlations with $D_{2/3}$ receptor binding and both general psychopathological and negative schizophrenic symptoms, as assessed by the Positive and Negative Syndrome Scale (PANSS) [25]. Therefore, the objective of the present study was to explore dopamine $D_{2/3}$ densities in the thalamus and midbrain in drug-naïve schizophrenic patients. In addition, we examined the patients' clinical status to evaluate the possibility of an association between $D_{2/3}$ binding and both the nature and severity of associated specific symptoms.

Materials and methods

This study is a reanalysis with new regions of interest (ROI) of the cohort of schizophrenic patients previously reported in Tuppurainen et al. 25. One of the previously reported patients is excluded from this reanalysis because of loss of data. The study was approved by the Kuopio University Hospital ethical committee. Written, informed consent was obtained from each patient and control volunteer after a full explanation of the study. Patients who met the ICD-10 criteria for either schizophrenia or schizophreniform disorder were recruited from hospitals and outpatient units in Kuopio, Finland. Six drug-naïve patients (four females, two males) aged 19–50 years (mean ± SD 33 ± 14 years) were included. Diagnoses were confirmed with the Structured Clinical Interview for the DSM-III-R [26] by a trained psychiatrist. The duration of illness ranged from 1 month to 3 years (mean 11 months). All patients were right-handed. Exclusion criteria were any organic brain disorder, alcohol and/or other drug abuse or previous antipsychotic drug treatment. The neuroleptic-naïve state was confirmed by clinical records and by interviews with both patients and proxy informants. Although none of the patients had ever used antipsychotic medications, two patients received small doses of benzodiazepines (diazepam 5 mg or oxazepam 15 mg) occasionally a few days before the scan. (The results of these patients did not differ from other patients.) None of the patients received other medications that might confound D_2 receptor binding measurements (such as antidepressants, beta-blockers or antiepileptic drugs). The clinical condition of the patients was evaluated by the PANSS [27], and mean scores were 84.7 (SD = 15.9) for total symptoms, 21.3 (SD = 2.7) for positive symptoms, 20.7 (SD = 6.6) for negative symptoms, and 42.7 (SD = 9.2) for the general psychopathological score.

Seven healthy, right-handed volunteers (four males and three females) of 19–42 years (mean ± SD 31±9 year) were used as controls in this study. The controls had no history of neuropsychiatric disorder or alcohol/drug abuse.

[^{123}I]Epidepride (185 MBq; supplied by MAP Medical Technologies Oy, Tikkakoski, Finland) was injected intravenously into the right antecubital vein. The single-photon emission tomography (SPET) scan was performed starting 30 min and completed 60 min after injection of the tracer (since the highest uptake in extrastriatal regions peaks at 45–60 min after injection of ligand) using a dedicated MultiSPECT 3 gamma camera with fan-beam collimators (Siemens Medical Systems Inc., Hoffman Estates, IL, USA). The energy window was centred on the photo peak of [^{123}I] (i.e., 148–170 keV). During 360° rotation (120° per camera head), 40 view/head scans were acquired in a 128 by 128 matrix (with a pixel size of 2.8 mm). The radius of rotation was 13 cm. The imaging resolution was 9–10 mm and a soft filter (Butterworth: cut-off frequency 0.4 cm^{-1} and order 5) was used in reconstruction to yield the images of low density receptors. This SPET imaging protocol was previously described in more detail by Kuikka et al. 28. No scatter correction was applied.

Transaxial slices (6 mm thick) were reconstructed and corrected for attenuation (Fig. 1). ROI were drawn onto the cerebellum (as a reference region = free + non-specific binding), and both the thalamus and the midbrain (=free + non-specific + specific binding) with the help of a reference atlas (Talairach & Tournoux 29]. The operator did not know whether or not the individual scan was from a patient or a control (Fig. 2). Specific binding of [^{123}I]epidepride in the ROI was calculated from the average count density from each region as (ROI−cerebellum)/cerebellum. The vermis was excluded from the cerebellar ROI. According to earlier experience, the cerebellum can be used in this way as a reference region [25]. Cerebellar count rates between patients and controls did not differ significantly ($P = 0.39$). The high affinity of [^{123}I]epidepride is optimal for imaging the relative low density of $D_{2/3}$ receptors in extrastriatal regions. In the basal ganglia, which have high $D_{2/3}$ receptor density, the ligand binding does not reach equilibrium. Therefore, measuring the striatal $D_{2/3}$ binding reliably is difficult.

Magnetic resonance imaging (MRI) was used to exclude neurostructural anomalies in patients with schizophrenia. These patients were scanned with a 1.5 T Siemens Vision camera (Erlangen, Germany) using a standard head coil and a tilted T_1–weighted coronal 3-D gradient echo sequence (MPRAGE: TR 10 ms, TE 4 ms, TI 250 ms, flip angle 12°, FOV 250 mm, matrix 256 by 192, 1 acquisition).

A univariate analysis of covariance (ANCOVA) with age as a covariate was performed to compare differences in dopamine $D_{2/3}$ receptor densities between schizophrenic patients and control individuals to exclude the possibility that the slight difference in mean ages might influence the results. Age was selected as a covariate because previous postmortem and neuroreceptor-specific imaging studies have demonstrated age-related reduction of dopamine $D_{2/3}$ receptor sites in striatal and extrastriatal brain re-

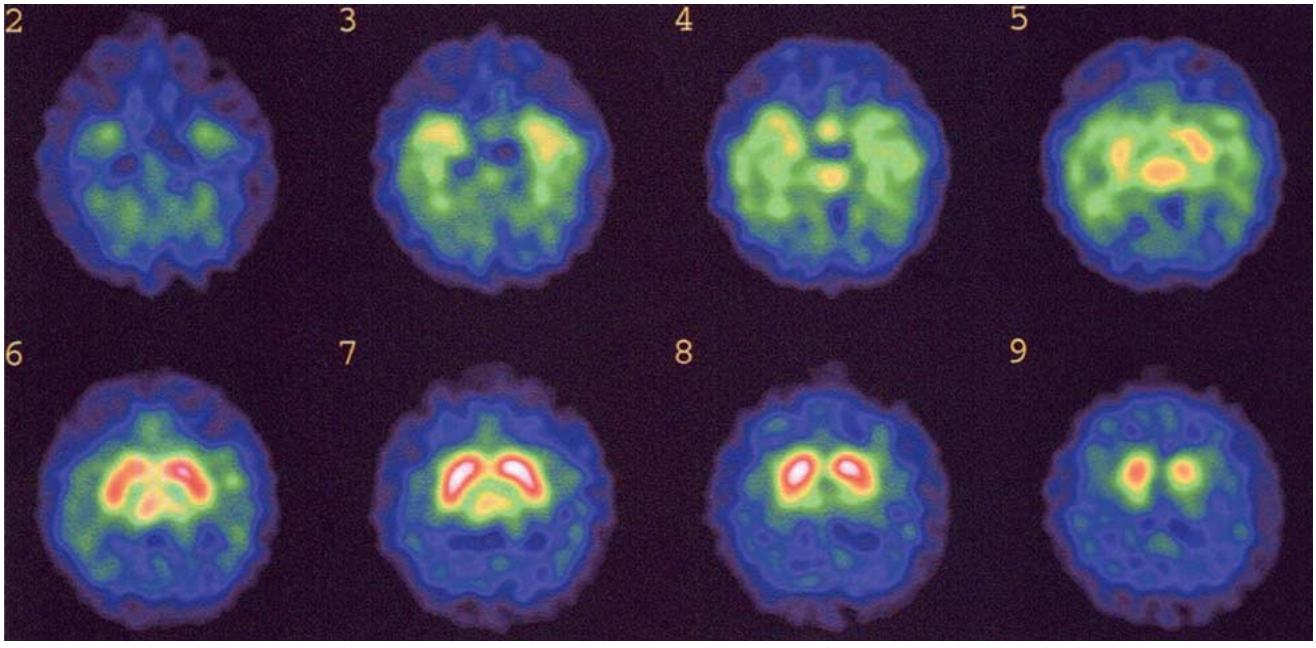

Fig. 1 [^{123}I]epidepride binding in the brain of a neuroleptic-naïve schizophrenic patient. Acquisition was started 30 min and completed 60 min after injection of tracer. The upper row illustrate dopamine $D_{2/3}$ binding in cerebellum, temporal poles and midbrain, and lower row that in thalamus and basal ganglia

gions [30, 31, 32]. Relationships between thalamic and nigral $D_{2/3}$ receptor densities, adjusted for age and the different dimensions of PANSS scores for the patients, were evaluated using Pearson's two-tailed correlation method, as were the age-adjusted cerebellar count rates between schizophrenics and healthy controls. A power analysis of binding values between groups was performed according to the methods described by Cohen [33].

Results

The specific binding values in the midbrain for the schizophrenic patients and healthy controls are shown in Fig. 3. The binding values (ml/ml; mean ± SD) in the midbrain (1.73 ± 0.13 vs. 2.07 ± 0.24, effect size = 1.71, $F = 8.34$, $P = 0.016$, ANCOVA) were lower in patients compared to the controls. There were no statistically significant differences in the thalamic $D_{2/3}$ receptor densities between the schizophrenic patients and controls (1.59 ± 0.23 vs. 1.74 ± 0.32, effect size = 0.51, $F = 0.73$, P = NS on the right; 1.66 ± 0.20 vs. 1.66 ± 0.25, effect size = 0.01, $F = 0.00$, P = NS on the left). A slight trend was seen towards a decrease in binding values of the schizophrenics in the right thalamus compared to controls. There were no statistical differences between the variance of $D_{2/3}$ density, either in the thalamus or in the midbrain among schizophrenic

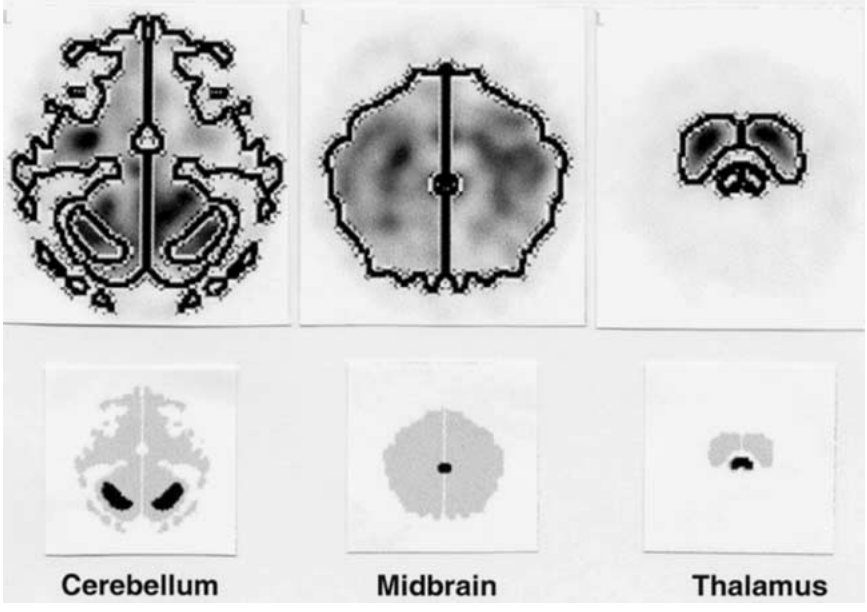

Fig. 2 Example of ROI analysis for the semi-quantitative calculation of specific- to non-specific binding ratios. Specific binding ratio = (ROI−cerebellum) / cerebellum. The cerebellar ROI is drawn onto slice 2 (Fig. 1), that of midbrain onto slice 4 and thalamus onto slice 6, respectively

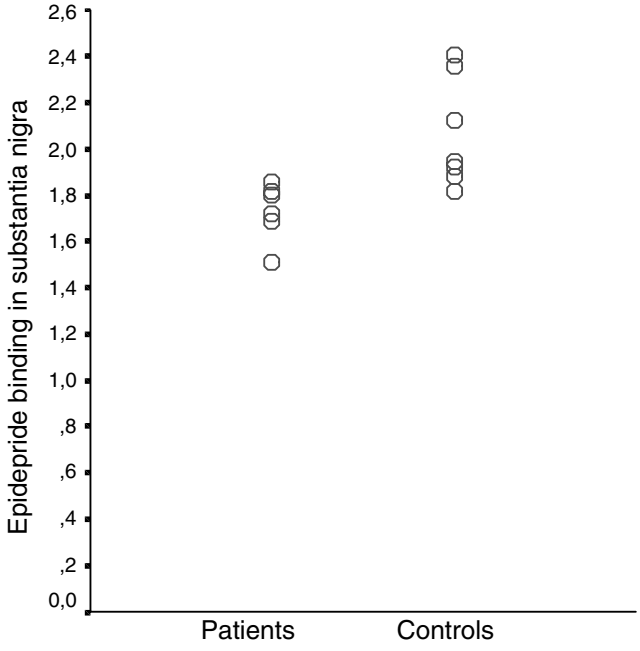

Fig. 3 A scatterplot of epidepride binding in the midbrain of controls (n = 7) and patients (n = 6)

patients vs. controls. We found no differences in binding values between male and female patients (P = 0.19 – 0.33) or control individuals (P = 0.26 – 0.82). Only one patient smoked and her binding values approached the mean binding values of the patient group (1.72 in the midbrain, 1.56 in the thalamus on the right and 1.75 on the left, respectively).

The clinical assessment was performed within the patient group where evident negative correlations were found in the thalamus between the PANSS general psychopathological score and [^{123}I]epidepride binding (r = −0.78, P = NS on the right; r = −0.92, P = 0.03 on the left). The correlations between [^{123}I]epidepride binding in the thalamus and the PANSS negative symptom scores (r = −0.48, P = NS on the right; r = −0.63, P = NS on the left) and positive symptom scores (r = −0.38, P = NS on the right; r = −0.41, P = NS on the left) were lower. In the left side, the $D_{2/3}$ density explained a substantial proportion of the variance in the general psychopathological score (r^2 = 85%), whereas the effect on the right side was smaller (r^2 = 60%). There were no remarkable correlations in the midbrain between [^{123}I]epidepride binding and different dimensions of the PANSS scores (positive symptom score: r = 0.66, negative symptom score: r = −0.31 and general psychopathological score: r = 0.28). No gross neuroanatomical anomalies or atrophy were observed in any of the MRI scans among schizophrenic patients.

Discussion

To our knowledge, this is the first study on dopamine $D_{2/3}$ binding in the midbrain of living schizophrenic patients. On the basis of the studies on the distribution of $D_{2/3}$ receptors in the human brain, it is evident that the binding in this region is attributable to substantia nigra [11, 34]. Although the dopaminergic projections originating from ventral tegmental area are located closely to the substantia nigra, D_2 receptors are nearly absent in the ventral tegmental area when compared to the substantia nigra [12, see figure 2; 35, see figure 7). This strongly suggests that the observed signal originates mainly from substantia nigra. These binding values were statistically lower in patients with schizophrenia compared to healthy controls, whereas differences in the thalamic $D_{2/3}$ densities did not reach statistical significance because of the relatively small sample sizes. A slight trend towards decreased binding values on the right thalamus in schizophrenic patients was observed when compared with controls, which is in line with previous PET studies [23, 24].

The small size of substantia nigra region and relatively low receptor density compared to that of the striatum make in vivo dopamine receptor studies difficult. A partial volume effect for explaining the results from the substantia nigra cannot completely be excluded, as it is not possible to measure the volume of the substantia nigra. Although [^{123}I]epidepride binding in the striatum has been reported to be sensitive to endogenous dopamine levels in the short term [36], amphetamine challenged dopamine release did not displace binding of [^{123}I]epidepride [37]. In addition recent study with primates showed no change in extrastriatal binding by endogenous dopamine with high-affinity radioligand [^{11}C]FLB 457 (the bromo analogue of epidepride) [38]. There is still some evidence for competitive effects of endogenous dopamine on epidepride binding in temporal cortex (but not in thalamus) after dopamine depletion [39]. Few recent studies with [^{11}C]FLB 457 have indicated that high-affinity ligand binding may be sensitive on dopamine competition after provocation by cognitive task or medication [40, 41]. The effect of endogenous dopamine on the results from the substantia nigra or the thalamus cannot totally be ruled out. In addition, our results are based on semi-quantitative analysis in which the specific- to non-specific binding ratio is calculated by assuming that the cerebellar count rates (=reference region) do not differ between the groups.

Our results on $D_{2/3}$ density in the substantia nigra are in accordance with previous neuroimaging studies that indicate decreased dopamine $D_{2/3}$ binding sites in other extrastriatal areas, e.g. the temporal and anterior cingulate cortices, in patients with schizophrenia [25, 42]. In the substantia nigra, dopamine D_2 receptors have been suggested to serve as autoreceptors that regulate the nigrostriatal dopamine pathway [11, 12]. On the other hand, the distribution of dopamine D_3 receptors in the striatum and substantia nigra is also fairly abundant and overlapping with D_2

receptors, whereas D_3 receptors are thought to be located postsynaptically [43, 44]. Previous results have demonstrated that the distribution of [^{123}I]epidepride in extrastriatal regions mainly represents the dopamine D_2 receptor subtype [34]. Thus, our finding suggests reduced number of D_2 autoreceptors in schizophrenic patients compared to healthy subjects in the substantia nigra. This may contribute to the dysregulation of dopamine function in the striatum of patients with schizophrenia [3, 45].

We observed distinct negative correlations in both sides of the thalamus (although the correlations did not reach statistical significance on the right due to small number of patients) between $D_{2/3}$ receptor density and general psychopathological symptom scores. Some functional studies previously reported a connection between decreased metabolic activity in the thalamus and both cognitive functions and negative symptoms in schizophrenic patients [19, 20, 21]. This is in line with a recent experimental study that relates informational processing and cognitive function to dopaminergic transmission in the thalamus [22]. Our findings agree with these observations and emphasize the significance of thalamo-cortical dopaminergic transmission in the pathophysiology of schizophrenia. Because of the limitations due to the semi-quantitative method used and the small sample size, our results on midbrain dopamine $D_{2/3}$ binding are considered provisional and require replication by future studies.

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