Dopamine D_2 Receptor Levels in Striatum, Thalamus, Substantia Nigra, Limbic Regions, and Cortex in Schizophrenic Subjects

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Background: Studies in schizophrenic patients have reported dopaminergic abnormalities in striatum, substantia nigra, thalamus, anterior cingulate, hippocampus, and cortex that have been related to positive symptoms and cognitive impairments.

Methods: [^{18}F]fallypride positron emission tomography studies were performed in off-medication or never-medicated schizophrenic subjects (n = 11, 6 men, 5 women; mean age of 30.5 ± 8.0 [SD] years; 4 drug-naive) and age-matched healthy subjects (n = 11, 5 men, 6 women, mean age of 31.6 ± 9.2 [SD]) to examine dopamine D_2 receptor (DA D_2r) levels in the caudate, putamen, ventral striatum, medial thalamus, posterior thalamus, substantia nigra, amygdala, temporal cortex, anterior cingulate, and hippocampus.

Results: In schizophrenic subjects, increased DA D_2r levels were seen in the substantia nigra bilaterally; decreased levels were seen in the left medial thalamus. Correlations of symptoms with ROI data demonstrated a significant correlation of disorganized thinking/nonparanoid delusions with the right temporal cortex ROI (r = .94, p = .0001), which remained significant after correction for multiple comparisons ($p <$ .03). Correlations of symptoms with parametric images of DA D_2r levels revealed no significant clusters of correlations with negative symptoms but significant clusters of positive correlations of total positive symptoms, delusions and bizarre behavior with the lateral and anterior temporal cortex, and hallucinations with the left ventral striatum.

Conclusions: The results of this study demonstrate abnormal DA D_2r-mediated neurotransmission in the substantia nigra consistent with nigral dysfunction in schizophrenia and suggest that both temporal cortical and ventral striatal DA D_2r mediate positive symptoms.

Key Words: Delusions, dopamine D_2 receptors, fallypride, hallucinations, schizophrenia, substantia nigra, thalamus

Abnormal dopaminergic neurotransmission has been implicated in the positive symptoms and cognitive deficits seen in schizophrenia (1–5). Recent studies suggest abnormal function of γ-aminobutyric acid (GABA)ergic/glutamatergic cortical microcircuits in schizophrenia, resulting in dysfunction of cortical pyramidal glutamatergic neurons (6), which provide a major excitatory afferent projection to the substantia nigra (7). Dysfunction of this projection results in nigral dysfunction and increased striatal dopamine (DA) release (8–10), which has been positively correlated with positive symptoms (11). Prefrontal cortical glutamatergic afferents to the ventral tegmental area (VTA) synapse directly on mesocortical DA neurons; it has been hypothesized that dysfunction of this projection leads to decreased cortical DA release (12), which is believed to be a factor in the cognitive impairments seen in schizophrenia (4). Because dopamine D_2 receptors (DA D_2r) directly modulate cortical GABAergic interneurons (13,14), ventral midbrain DA neurons (15,16), and DA release in striatal and extrastriatal regions (17), DA D_2r are of considerable interest in schizophrenia.

Consistent with the hypothesis of decreased cortical DA release in schizophrenia, postmortem studies have reported decreased dopaminergic innervation in medial temporal cortex, dorsolateral prefrontal cortex, and hippocampus (18–20) and dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC) levels in the anterior cingulate (21). Some imaging studies of extrastriatal DA D_2r in schizophrenic subjects have reported decreased DA D_2r levels in the anterior cingulate and temporal cortex, but most have not (22–27); the most frequent finding is decreased medial thalamic DA D_2r levels (24–26). Although there have been variable results, a recent study of DA D_1r in schizophrenic subjects reported increased frontal cortical levels that were negatively correlated with performance on a working memory task (28–30). The increased DA D_1r levels were interpreted as being consistent with decreased frontal cortical DA levels. Postmortem studies of dopaminergic function in the substantia nigra in schizophrenic subjects have reported increased levels of tyrosine hydroxylase (31), tyrosine hydroxylase messenger RNA (mRNA) (32), homovanillic acid (31), and DA D_2r (33) consistent with nigral dysfunction. Imaging studies have largely failed to examine substantia nigra DA D_2r. Both postmortem and imaging studies have reported increased striatal DA synthesis, DA levels, and DA release, which has been correlated with positive symptoms (34–41). In contrast to postmortem studies that have reported increased striatal DA D_2r levels (42,43), most but not all imaging studies of striatal DA D_2r have reported unaltered levels in schizophrenia (44–46). However, one imaging study of striatal DA D_2r performed before and after DA depletion with alphamethylparatyrosine demonstrated normal levels before DA depletion but increased DA D_2r levels after depletion consistent with both increased striatal DA release and increased total DA D_2r levels (36). The discrepancy between postmortem studies and imaging studies with benzamide radioligands might be due to the occupancy of striatal DA D_2r by increased levels of extracellular DA. Overall, the available post-

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mortem and imaging data are consistent with the hypothesis of decreased cortical DA release, nigral DA neuronal dysfunction, and increased striatal DA release in schizophrenia.

Previous imaging studies of DA D_2r in medication-free schizophrenic subjects have evaluated either striatal or extrastriatal DA D_2r levels (22–27,44,45). In the current study, positron emission tomography (PET) with [^{18}F]fallypride was used. [^{18}F]Fallypride is a very high-affinity, specific benzamide PET radioligand for the DA D2 receptor (K_D = .03 nmol/L) and is the only currently available radioligand that allows estimation of both striatal and extrastriatal DA D_2r levels (22,24,27,44-48). Given the hypothesis of nigral dysfunction in schizophrenia (1,8–10,12), the lack of previous imaging studies of the substantia nigra DA D_2r, postmortem findings consistent with nigral dysfunction (31–33), and the ability of PET [^{18}F]fallypride studies to estimate nigral DA D_2r levels (48,49), we specifically examined this region. Other regions previously reported to have altered DA D_2r levels—the anterior cingulate, temporal cortex, and medial thalamus (22–26)—were examined. Because significant correlations of symptoms with regional DA D2r levels have been reported (22–27), correlations of positive and negative symptoms with regional DA D_2r levels were assessed.

Methods and Materials

Subjects

This study was conducted under protocols approved by the Vanderbilt University and Centerstone Mental Health Center institutional review boards. All subjects were judged capable of giving informed consent by a senior research psychiatrist and provided informed consent for this study. Subjects meeting the DSM-IV criteria (American Psychiatric Association, 1994) and Research Diagnostic Criteria (50) for the diagnosis of schizophrenia between the ages of 18 and 45 were recruited. The diagnosis of schizophrenia was established by the Structured Clinical Interview for DSM IV Axis I disorders (51) and checklist. Schizophrenic subjects (n = 11, 6 men, 5 women; mean age of 30.5 ± 8.0 [SD] years and age range of 20–45 years) were either never treated (n = 4) or were off-medication for at least 3 weeks (Table 1). The Brief Psychiatric Rating Scale (BPRS) (6 item scales), Scale for the Assessment of Positive Symptoms (SAPS), and Scale for Assessment of Negative Symptoms (SANS) were administered to each subject; mean total BPRS, SAPS, and SANS scores were 28.8 ± 7.0 (SD), 9.8 ± 3.1 (SD), and 9.4 ± 4.0 (SD), respectively. Age-matched healthy subjects (n = 11, 5 men, 6 women, mean age of 31.6 ± 9.2 [SD] years and age range of 21–45 years) were recruited as well. Significant medical conditions and previous or current substance abuse were exclusion criteria for all subjects.

Table 1. Demographic Data for Off-Medication Schizophrenic Subjects

Subject Number	Gender	Age	Medication-Free Period	Previous Medications	BPRS Score (6-item scale)
1	F	36	3 weeks	quetiapine	30
2	F	32	9 weeks	quetiapine	32
3	M	22	5 weeks	olanzapine	38
4	M	20	Never Medicated	NA	27
5	F	36	21 weeks	olanzapine	40
6	F	39	10 weeks	olanzapine	19
7	M	22	Never Medicated	NA	32
8	F	35	Never Medicated	NA	18
9	M	23	40 weeks	olanzapine	30
10	M	45	Never Medicated	NA	29
11	M	26	3 weeks	olanzapine	22

BPRS, Brief Psychiatric Rating Scale.

Data Acquisition and Analysis

Magnetic resonance imaging (MRI) scans of the brain were performed with a GE 1.5-T Signa LXi MRI scanner (GE Healthcare, Waukesha, Wisconsin). High-resolution T1-weighted gradient echo acquisitions in the sagittal plane (1.2–1.3-mm-thick slices) and coronal planes (1.4–1.5-mm-thick slices) and axial spin density-weighted and T2 weighted (3-mm-thick slices) acquisitions were obtained. The PET scans were performed with a GE Advance PET scanner in the three-dimensional acquisition mode. [^{18}F]Fallypride (4–5 mCi, specific activity >2000 Ci/mmol, maximum mass dose of <2.5 nmol) was injected intravenously over a 20-sec period; serial scans of increasing duration were obtained for 210 min, allowing stable estimates of binding potentials in all regions (47–49). A measured attenuation correction was used.

Serial PET scans were co-registered to each other and to thin section T1-weighted MRI images with a rigid-body, mutual information algorithm (52,53) and reoriented to the anterior commissure–posterior commissure (ACPC) line. Regions of interest (ROIs) were identified on thin section T1 weighted MRI images and transferred to co-registered PET studies. The putamen and caudate were manually drawn by a neuroradiologist (RMK) on axial slices from 2 to 12 mm above the ACPC line. The ventral striatum was defined with the criteria of Mawlawi *et al.* (54). Sobel filtering was performed on high-resolution gradient echo MRI images of the brain (55) but did not provide reliable boundaries for delineation of the dorsomedial thalamus and pulvinar. We used anatomic landmarks to delineate the medial thalamus and posterior thalamus, which approximated the boundaries of the dorsomedial thalamus and pulvinar (56). The medial thalamus was delineated on slices from 2 to 12 above the ACPC line; the posterior border was the coronal plane of the posterior commissure, the medial border was the midline, the anterior boundary was the foramen of Monro, and the lateral border extended up to 1 cm from the midline. The anterior border of the posterior thalamus was the coronal plane of the posterior commissure, the medial and posterior borders were the edge of the thalamus as it projects into the quadrigeminal plate cistern, and the lateral border was the posterior limb of the internal capsule. The substantia nigra/VTA is located in the ventral midbrain 9–14 mm below the ACPC line (56) and can be readily visualized in the midbrain on PET [^{18}F]fallypride scans (57). Substantia nigra ROIs were manually drawn to adjust for inter-individual variability by a neuroradiologist (RMK); the intersubject coefficient of variation for the substantia nigra region was 8.7% (57). The amygdala can be visualized on MRI scans just anterior to the tip of the temporal horn of the lateral ventricle and deep to the uncus (57); the amygdala is located 6–20 mm below the ACPC line, 12–28 mm lateral to the midline, and from 2 to 12 mm behind the plane of the anterior commissure (56). To decrease partial voluming from the striatum, amygdala ROIs were drawn on MRI images from 10 to 16 mm below the plane of the ACPC. Temporal cortical ROIs were manually drawn on axial MRI images from 35 to 25 mm below the ACPC. Our previous studies have shown excellent inter-subject reliability for these ROIs (i.e., inter-subject coefficients of variation of 6.8%–15.9%) (57). The anterior cingulate was delineated as extending from superior to the axial plane through the ACPC in the pregenual region superiorly and