Increased Synaptic Dopamine Function in Associative Regions of the Striatum in Schizophrenia

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Context: A long-standing version of the dopamine hypothesis of schizophrenia postulates that hyperactivity of dopaminergic transmission at D2 receptors in the limbic striatum is associated with the illness and that blockade of mesolimbic D2 receptors is responsible for the antipsychotic action of D2 receptor antagonists.

Objective: To localize dopaminergic hyperactivity within the striatum in schizophrenia.

Design: Case-control study.

Setting: Inpatient research unit.

Participants: Eighteen untreated patients with schizophrenia and 18 healthy control subjects matched for age, sex, ethnicity, parental socioeconomic status, cigarette smoking, and weight.

Main Outcome Measures: Percentage change in dopamine D2 receptor availability in striatal subregions within each subject measured by positron emission tomography with carbon 11–labeled raclopride before and during pharmacologically induced dopamine depletion.

Results: In the associative striatum, acute dopamine depletion resulted in a larger increase in D2 receptor availability in patients with schizophrenia (mean [SD], 15% [7%]) than in control subjects (10% [7%], \( P = .045 \)), suggesting higher synaptic dopamine concentration. Within the associative striatum, this effect was most pronounced in the precommissural dorsal caudate (15% [8%] in patients vs 9% [8%] in controls, \( P = .03 \)). No between-group differences were observed in the limbic and sensorimotor striatum.

Conclusions: These findings suggest that schizophrenia is associated with elevated dopamine function in associative regions of the striatum. Because the precommissural dorsal caudate processes information from the dorsolateral prefrontal cortex, this observation also suggests that elevated subcortical dopamine function might adversely affect performance of the dorsolateral prefrontal cortex in schizophrenia. On the other hand, the absence of a group difference in the limbic striatum brings into question the therapeutic relevance of the mesolimbic selectivity of second-generation antipsychotic drugs.

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CHZIZOPHRENIA IS A CHRONIC mental illness characterized by disturbances of thought, perception, volition, and cognition. Schizophrenia typically emerges during late adolescence, and the course of the illness is usually characterized by alternating episodes of illness exacerbation and partial remission.1 Manifestations of the illness are commonly divided into positive (delusions, hallucinations, and thought disorganization), negative (lack of drive and motivation, alogia, passivity, and social withdrawal), and cognitive (poor performance on cognitive tasks involving attention, memory, and executive function) symptoms.2,3

The prognosis of schizophrenia has dramatically improved since the introduction of antipsychotic medications in the late 1950s.4 Because all antipsychotic drugs are antagonists at the D2 receptor,5,6 an alteration of dopamine (DA) transmission at this receptor has long been suspected of playing a role in the pathophysiologic mechanism of schizophrenia. Specifically, excess D2 transmission has been proposed to underlie positive symptoms because these symptoms respond better than negative or cognitive symptoms to D2 receptor blockade (for references and review, see Davis et al7).

With advances in brain imaging techniques, direct evidence suggestive of dysregulation of striatal DA transmission in schizophrenia has emerged. Studies have documented an increase in the striatal accumulation of fluorine 18–labeled fluorodopa in schizophrenia,8,14 consistent with increased activity of dopa-decarboxylase, an enzyme involved in DA synthesis. Investigation of DA synaptic levels was made possible by imaging the competition between DA and radiotracers for binding to D2 receptors. Three of 3 studies using this approach have reported an increase in am-

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PET protocol

Subjects underwent 2 measurements of D2 receptor BPND with PET, [11C]raclopride, and the sustained equilibrium–constant infusion technique.6 The first scan was obtained in control conditions (baseline scan) on day 1 of the study. The second scan was obtained on day 3, during DA depletion induced by oral administration of α-MPT, dosed on a sliding scale by subject weight 4 times daily for 2 days. Thus, 2 measures of BPND were obtained in each subject: at baseline (BPND BASE) and in the depleted state (BPND DEPL). On both days, [11C]raclopride was administered as a priming bolus followed by constant infusion for 80 minutes. The bolus to infusion ratio was 105 minutes (i.e., 53% of the dose was given in the bolus). [11C]Raclopride was delivered in a 60-mL normal saline solution. A bolus dose of 30 mL was administered over 2 minutes via a pump (Gemini PC-1; IMED, San Diego, California). After the bolus, the pump was reset to deliver 25 mL at 0.3 mL/min for the remaining 80 minutes. This infusion protocol induces a state of sustained binding equilibrium, starting at about 45 minutes.15

Imaging was performed with a PET camera (ECAT EXACT HR+; Siemens/CTI, Knoxville, Tennessee) that acquires 63 sections covering an axial field of view of 15.5 cm (axial sampling of 2.46 mm). The 3-dimensional mode in plane and axial resolutions are 4.4 and 4.1 mm full-width half-maximum at the center of the field of view, respectively. Emission data were collected in the 3-dimensional mode as 8 successive frames of 5 minutes’ duration collected from 40 to 80 minutes after the start of the [11C]raclopride infusion.

α-MPT administration

The regimen of α-MPT administration was selected to provide and maintain significant inhibition of tyrosine hydroxylase activity.37 The α-MPT was given for 2 days because this duration of treatment is adequate to produce marked DA depletion but too short to induce significant D2 receptor upregulation (see discussion in Laruelle et al19). The first α-MPT dose was given on the evening of day 1 (8 PM). On day 2, α-MPT was administered at 7 AM, noon, 6 PM, and 11 PM. On day 3, α-MPT was given at 7 AM, noon, and 1 hour before the beginning of the second scanning session (5 PM).

The dose of α-MPT was adjusted to subjects’ weight, according to a sliding scale (30 kg and 113 kg are the weight limits defined by inclusion criteria): 30 to 58 kg, 750 mg; 59 to 75 kg, 1000 mg; 76 to 92 kg, 1250 mg; and 93 to 115 kg, 1500 mg. With the use of this scale, each dose was between 12.9 mg/kg

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and 16.9 mg/kg for all subjects. To prevent the formation of α-MPT crystals in the urine, subjects were instructed to drink at least 4 L of fluids per day, starting the day before the study, and fluid intake was carefully monitored. Urinalysis was performed daily. Clinical evaluation, including orthostatic blood pressure monitoring, was performed 4 times a day. Trough plasma α-MPT levels were measured 4 hours after the seventh dose by means of gas chromatography–mass spectrometry.

**IMAGE ANALYSIS**

Image analysis was performed with image processing and analysis software (MEDx; Sensor Systems Inc, Sterling, Virginia) as described previously. PET data were coregistered to a T1-weighted high-resolution magnetic resonance image acquired on a 1.5-T imaging system (Signa Advantage; General Electric, Milwaukee, Wisconsin). Regions of interest (ROIs) were drawn on each individual's magnetic resonance image and applied to the coregistered PET images. The striatum was divided into 5 anatomic ROIs comprising 3 functional subdivisions, as described previously. The ROIs included the ventral striatum (VST), the precommissural dorsal caudate (preDCA), the precommissural dorsal putamen, the postcommissural caudate, and the postcommissural putamen. Activities from left and right regions were averaged.

On the basis of their cortical and subcortical connections, the preDCA, precommissural dorsal putamen, and postcommissural caudate were classified functionally as belonging to the associative striatum (AST), the VST captured the limbic striatum (LST), and the postcommissural putamen captured the sensorimotor striatum. The cerebellum was used as the region of reference to estimate nonspecific binding.

Specific binding was defined as the difference between activity in the ROI (AROI) and activity in the cerebellum (ACER). The binding potential relative to nonspecific binding (BPND) was defined as follows:

$$\frac{A_{ROI} - A_{CER}}{A_{CER}} = \text{BPND} = f_{ND} \times \frac{B_{MAX}}{K_D \left(1 + \frac{f_{ND}}{K_s}\right)}$$

where $f_{ND}$ is the fraction of free plus nonspecifically bound ligand in brain, $B_{MAX}$ is the maximal number of binding sites, $1/K_D$ is the affinity of [11C]raclopride for D2 receptors, $F_{DS}$ is the temporal and spatial average concentration of free synaptic DA in the vicinity of D2 receptors, and $K_s$ is the inhibition constant of DA for [11C]raclopride at the D2 receptor.

The α-MPT–induced increase in BPND was calculated as the difference between $\text{BPND}_{\text{BASE}}$ and $\text{BPND}_{\text{DEPL}}$, expressed as a percentage of $\text{BPND}_{\text{BASE}}$. Because $F_{DS}$ during the depleted condition is negligible compared with $K_s$, the increase in $\text{BPND}_{\text{DEPL}}$ by α-MPT is linearly related to baseline $F_{DS}$ by $F_{DS} \times K_s$ ($a = 1$). Therefore, the relative increase in $\text{BPND}_{\text{DEPL}}$ from baseline to the depleted state provides an index of the DA synaptic concentration during the baseline state.

**STATISTICAL ANALYSIS**

Between-group comparisons were performed by factorial analysis of variance or repeated-measures analysis of variance with group × effect interaction, as appropriate. Relationships between continuous variables were analyzed with the Pearson product moment correlation coefficient. A probability value of .05 was selected as the significance level.

**RESULTS**

**GROUP COMPOSITION**

Twenty-two patients and 22 controls were recruited for this study. Eighteen patients and 18 controls completed the protocol. Reasons for noncompletion (n=8) included cyclopron failure on the day of the second scan (n=1) and intolerance of the adverse effects of α-MPT (n=7), resulting in withdrawal from the study. Common adverse effects included sedation, orthostatism, tremor, irritability, and bradykinesia. These effects spontaneously resolved within 12 hours of the last α-MPT administration. Uncommon adverse effects included acute dystonia (observed in 1 subject) that resolved within minutes after diphenhydramine hydrochloride administration. Crystalluria was not observed in this study.

Completers were matched for age, sex, ethnicity, parental socioeconomic status, cigarette smoking, and weight (Table 1). Among the 18 patients, 6 were antipsychotic-naive and experiencing a first episode of illness. Twelve patients were chronically ill and had been previously treated with antipsychotic drugs. In the previously treated group, 4 patients had not received antipsychotic drugs for more than 1 year. In the remaining 8 patients, the mean (SD) interval between the last antipsychotic administration and the first scan was 110 (96) days (minimum, 20 days; maximum, 300 days). These previously treated patients were experiencing an episode of illness exacerbation at the time of recruitment and were admitted to the hospital for clinical reasons. Total PANSS scores at baseline were 78.6 (20.6) (with these and subsequent values given as mean [SD]) in the patient group.

**EXPERIMENTAL PARAMETERS**

No between-group differences were observed in [11C]raclopride radiolig and mass dose or in α-MPT dose or plasma levels (Table 2).

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**Table 1. Demographic and Clinical Variables**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Subjects (n=18)</th>
<th>Patients With Schizophrenia (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29 (7)</td>
<td>29 (8)</td>
<td>&gt;.99</td>
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<td>Sex, No./M/F</td>
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<td>13/5</td>
<td>&gt;.99</td>
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<td>African American</td>
<td>7</td>
<td>7</td>
<td>&gt;.99</td>
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<tr>
<td>Hispanic</td>
<td>4</td>
<td>4</td>
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<td>Smoker, No./yes/no</td>
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<td>4/14</td>
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<tr>
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<td>Socioeconomic statusa</td>
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<tr>
<td>Parental</td>
<td>38 (13)</td>
<td>38 (13)</td>
<td>.94</td>
</tr>
<tr>
<td>Subject</td>
<td>31 (13)</td>
<td>25 (13)</td>
<td>.18</td>
</tr>
</tbody>
</table>

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The relationship between the striatum as a whole, a trend-level difference was observed between severity of negative symptoms at baseline and 

**NOTE**

The increase magnitude of $\Delta B_{PD}$ in the AST is best explained by a higher occupancy of D$_2$ receptors by DA in patients with schizophrenia than in controls during the baseline scan. If $\alpha$-MPT–induced DA depletion were complete, this increase in D$_2$ receptor occupancy would indicate that DA occupies 8% (SD, 7%) of AST D$_2$ receptors in controls vs 13% (6%) in patients with schizophrenia. The $\alpha$-MPT regimen used in this study is estimated to result in about 70% to 80% depletion of striatal DA. At 4 g/d, $\alpha$-MPT induces 70% depletion in cerebrospinal fluid homovanillic acid, and the magnitude of DA depletion is expected to be larger than that of homovanillic acid depletion. Furthermore, at least 80% DA depletion or 80% D$_2$ receptor blockade is needed to produce extrapyramidal symptoms, which were present at a moderate level in most of the subjects.

The conclusion that occupancy of AST D$_2$ receptors by DA is increased in patients with schizophrenia compared with controls is valid even if the depletion is incomplete (see discussion in Abi-Dargham et al$^{24}$), provided that the relative magnitude of DA depletion is comparable between groups. This assumption is supported by the observation of similar plasma $\alpha$-MPT levels in both groups, by the fact that the range of $\alpha$-MPT plasma concentration observed in this study provides a high degree of tyrosine hydroxylase inhibition, and by the fact that the extent of DA depletion is expected to be larger than that of homovanillic acid depletion. Furthermore, at least 80% DA depletion or 80% D$_2$ receptor blockade is needed to produce extrapyramidal symptoms, which were present at a moderate level in most of the subjects.

The relationship between $\Delta B_{PD}$ and baseline positive and negative symptoms was investigated in the patient group. No significant relationship was observed between severity of positive symptoms at baseline and $\Delta B_{PD}$ in any of the 5 subregions. No significant relationship was observed between severity of negative symptoms at baseline and $\Delta B_{PD}$ in preDCA, precommisural dorsal putamen, postcommisural caudate, or postcommisural putamen. A significant inverse relationship was observed between severity of negative symptoms at baseline and $\Delta B_{PD}$ ($r^2=0.31, P=.01$). Among the PANSS negative subscale components, the item capturing passivity, apathy, and social withdrawal was the best correlated with low DA tone in the VST ($r^2=0.47, P=.001$).

**EFFECT OF PREVIOUS ANTIPSYCHOTIC TREATMENT**

The results of this study suggest that DA occupies a greater proportion of D$_2$ receptors in untreated patients with schizophrenia than in matched control subjects in the AST during the first episode of illness and subsequent episodes of illness exacerbation. In contrast, no difference was observed between patients and controls in D$_2$ receptor occupancy by DA in the LST or in the sensorimotor striatum. In preDCA, acute DA depletion resulted in 9% (8%) and 15% (8%) increases in D$_2$ receptor availability in control subjects and patients with schizophrenia, respectively, suggesting that the temporal and spatial average synaptic DA concentration in this region is almost double that of healthy controls.

**METHODOLOGIC CONSIDERATIONS**

The increased magnitude of $\Delta B_{PD}$ in the AST is best explained by a higher occupancy of D$_2$ receptors by DA in patients with schizophrenia than in controls during the baseline scan. If $\alpha$-MPT–induced DA depletion were complete, this increase in D$_2$ receptor occupancy would indicate that DA occupies 8% (SD, 7%) of AST D$_2$ receptors in controls vs 13% (6%) in patients with schizophrenia. The $\alpha$-MPT regimen used in this study is estimated to result in about 70% to 80% depletion of striatal DA. At 4 g/d, $\alpha$-MPT induces 70% depletion in cerebrospinal fluid homovanillic acid, and the magnitude of DA depletion is expected to be larger than that of homovanillic acid depletion. Furthermore, at least 80% DA depletion or 80% D$_2$ receptor blockade is needed to produce extrapyramidal symptoms, which were present at a moderate level in most of the subjects.

The conclusion that occupancy of AST D$_2$ receptors by DA is increased in patients with schizophrenia compared with controls is valid even if the depletion is incomplete (see discussion in Abi-Dargham et al$^{25}$), provided that the relative magnitude of DA depletion is comparable between groups. This assumption is supported by the observation of similar plasma $\alpha$-MPT levels in both groups, by the fact that the range of $\alpha$-MPT plasma concentration observed in this study provides a high degree of tyrosine hydroxylase inhibition, and by the fact that the between-group difference was regionally selective. This conclusion also requires that no significant upregulation of D$_2$ receptors occurred during the acute DA depletion, an assumption confirmed in rodent studies.$^{39}$ Finally, it is important to note that changes in $^{[1]}$raclopride BPND following changes in synaptic DA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>Patients With Schizophrenia Value</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline $[^{11}]$raclopride scan</td>
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<td></td>
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<tr>
<td>Radiation dose, mCi</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mass dose, µg</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$[^{11}]$raclopride scan in depleted state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation dose, mCi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass dose, µg</td>
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<td></td>
<td></td>
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<tr>
<td>$\alpha$-Methylparatyrosine treatment</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dose, mg $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Plasma levels, ng/mL</td>
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</tr>
</tbody>
</table>

SI conversion factor: To convert millicuries to megabecquerels, multiply by 37.

$\alpha$-MPT EFFECTS ON $[^{11}]$ RACLOPRIDE BP$_{PD}$

No significant differences were observed between control subjects and patients with schizophrenia in baseline $[^{11}]$ raclopride BP$_{PD}$ in any region (Table 3). The D$_2$ receptor availability was significantly higher after $\alpha$-MPT exposure than at baseline in all regions (repeated-measures analysis of variance, \(P<.001\); Table 3).

Table 3 and Figure 2 report the effect of $\alpha$-MPT on $[^{11}]$ raclopride BP$_{PD}$ ($\Delta B_{PD}$) by group in striatal subregions and in the striatum as a whole. No between-group differences were observed in $\Delta B_{PD}$ in the VST and the sensorimotor striatum ($P=.56$ and .32, respectively). In the AST, $\Delta B_{PD}$ was significantly larger in patients than controls ($P=.045$). Among the AST subregions, a significant between-group difference was observed in the preDCA ($P=.03$), but not in the other regions. In the striatum as a whole, a trend-level difference was observed between the groups ($P=.07$). The $\alpha$-MPT plasma levels were not correlated with $\Delta B_{PD}$, either in the regions or in the striatum as a whole ($r^2<0.03$).

$\alpha$-MPT EFFECT ON SYMPTOMS

Exposure to $\alpha$-MPT induced a significant reduction (−15% [15%]) in the severity of positive symptoms, a significant increase in the severity of negative symptoms (+16% [31%]), and no changes in the general pathology subscale or in the total PANSS rating (Table 4).
levels might be more complex than accounted for by a simple binding competition model (for review and discussion, see Laruelle18).

COMPARISON WITH THE PREVIOUS STUDY

No between-group difference in baseline D2 receptor availability was seen in this or the previous α-MPT study carried out with single-photon emission computed tomography (SPECT) and iodobenzamide labeled with iodine 123,24 an observation in agreement with most imaging reports in untreated patients with schizophrenia (for review and references, see Laruelle15). This study, in line with the previous α-MPT study,24 confirms that acute DA depletion led to a higher increase in D2 receptor availability in patients than in controls. In contrast to the previous α-MPT study,24 D2 receptor availability measured during DA depletion was not significantly higher in patients than controls because of large between-subject variability in both groups. These data lend further support to the conclusion that, in schizophrenia, elevated D2 receptor transmission is due to increased stimulation of D2 receptors by DA rather than abnormally high expression of D2 receptors.

At the level of the striatum as a whole, the results of the present study performed with PET and [11C]raclopride were comparable to the results of the previous study. In that study, the α-MPT regimen resulted in an increase in 9% (7%) of [11C]iodobenzamide BPND in control subjects compared with 19% (11%) in patients with schizophrenia (P = .003). In the SPECT study, the difference between patients and controls was significant in the striatal region, whereas in this study it was present only at trend level. This difference is not likely to be due to differences in the patient samples: both groups were recruited from the same hospital ward and exhibited similar levels of symptom severity. Also, the mean doses and α-MPT plasma levels were similar in the 2 studies. Thus, the difference between the 2 studies might simply be related to sampling variability. Also, the striatal ROIs drawn on SPECT images are more rostral and dorsal than the striatal ROIs drawn on magnetic resonance images in the PET study. As a result, the striatal SPECT region might be more weighted toward the AST, the striatal subregion found to have a significant group difference in the PET study.

REGIONAL LOCALIZATION

The LST ΔBPND was similar in patients and controls, an observation that did not support the long-standing hypothesis of a DA elevation in the LST in schizophrenia. The only finding in the LST was that of a correlation between low ΔBPND and severity of negative symptoms, suggesting that low DA activity in this region might contribute to negative symptoms. In contrast, a group difference in ΔBPND was observed in the AST and was more pronounced in the rostral and dorsal part of the caudate nucleus (preDCA). Because our a priori hypothesis was that DA levels would be more elevated in LST than in other regions, this result was unexpected, and replication will be needed before asserting that the increase in DA levels in schizophrenia in AST is a robust finding.
patients with schizophrenia was not a long-term consequence of previous exposure to D2 receptor antagonists because the effect was similar in previously treated patients and antipsychotic-naive patients. Thus, this factor appears to be associated with the illness rather than its treatment. No relationship was found between levels of synaptic DA in AST and severity of positive symptoms rated cross-sectionally by the PANSS. In a previous study of striatal DA transmission dysfunction in schizophrenia that used the amphetamine challenge, the magnitude of DA dysregulation was found to be better predicted by the acuity of the positive symptoms rather than their severity.44 This temporal dimension of the positive symptoms is not captured by the PANSS.

The hypothesis was formulated in the early 1970s,45-49 notably in an influential article by Stevens.50 As pointed out by Lidsky,31 the striatum was conceptualized at that time as being mostly involved in motor control. The mesolimbic hypothesis provided “conceptual relief” to the DA hypothesis of schizophrenia because the territories innervated by the mesolimbic DA system were known to be involved in modulation of drive, affect, and memory, dimensions more related to psychiatric symptoms than the motor functions ascribed to the striatum.

This widely held hypothesis also implied that blockade of D2 receptors in the VST was responsible for the antipsychotic effect, whereas blockade of these receptors in nigrostriatal pathways was associated only with undesirable motor side effects. This hypothesis led to the view that a “mesolimbic selectivity” was a desirable property in the development of new antipsychotic drugs. Indeed, at low doses, most “atypical” or “second-generation” antipsychotic drugs show a dose-related selectivity for affecting the firing of A10 vs A9 neurons and for inducing gene expression in the nucleus accumbens vs the corpus striatum.52-58

Nevertheless, it is not yet established whether the mesolimbic-selective effects of these drugs observed at low doses in animals are relevant at the doses used in clinical settings.59-62 Furthermore, the therapeutic superiority of “second-generation” antipsychotic drugs has recently been questioned by a number of clinical trials.63-65 An important consequence of this study is the proposition that the “mesolimbic” selectivity of second-generation antipsychotic drugs might not be relevant to their therapeutic effectiveness because the primary site of antipsychotic action related to D2 receptor blockade might be the AST. Regarding the LST, the study suggests that, if anything, low DA tone in the VST might be associated with severity of negative symptoms (passivity and social withdrawal). This observation is consistent with the role of limbic DA in reward66 and with the general lack of effectiveness of antipsychotic drugs on these symptoms.

It is now well established that the dorsal striatum, particularly the caudate nucleus, is involved in learning, habituation, memory, attention, motivation, emotion, and volitional behavior.67-70 Furthermore, the preDCA is the area of the striatum that receives the largest corticostriatal projections from the dorsolateral prefrontal cortex (DLPFC)71-73 (Figure 3), the neocortical area most implicated in the pathophysiologic mechanism of schizophrenia. The D2 receptors in the striatum modulate corticostriatal synapses onto medium spiny neurons and, therefore, the flow of information within corticostriatal loops.74-79 The human AST also receives convergent inputs from limbic-related cortical regions and therefore supports some integrative functions ascribed to the nucleus accumbens in rodents.80,81 Thus, the AST, particularly the preDCA, is in a unique position to integrate information from multiple regions and to regulate circuitry affecting DLPFC function.

**Table 4. Effect of α-MPT on Symptoms**

<table>
<thead>
<tr>
<th>PANSS</th>
<th>Baseline</th>
<th>DA Depleted</th>
<th>Change, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive subscale</td>
<td>21.72 (7.12)</td>
<td>18.39 (6.77)</td>
<td>-15 (15)</td>
<td>&lt;.001 a</td>
</tr>
<tr>
<td>Negative subscale</td>
<td>17.17 (5.99)</td>
<td>19.00 (5.56)</td>
<td>16 (31) a</td>
<td>.048 a</td>
</tr>
<tr>
<td>General pathology subscale</td>
<td>39.72 (10.06)</td>
<td>39.00 (10.33)</td>
<td>-1 (12)</td>
<td>.55</td>
</tr>
<tr>
<td>Total</td>
<td>78.61 (20.63)</td>
<td>76.39 (20.46)</td>
<td>-2 (11)</td>
<td>.29</td>
</tr>
</tbody>
</table>

Abbreviations: α-MPT, α-methylparatyrosine; DA, dopamine; PANSS, Positive and Negative Syndrome Scale.

Table 5. Effect of DA Depletion on D2 Receptor Availability in Antipsychotic-Naive and Antipsychotic-Free Previously Treated Patients

<table>
<thead>
<tr>
<th>Functional Subdivision</th>
<th>ROI</th>
<th>Drug Free</th>
<th>Drug Naive</th>
<th>P Value</th>
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<tbody>
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<td>LST</td>
<td>VST</td>
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<tr>
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<td>preDCA</td>
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<tr>
<td>PreDPU</td>
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<tr>
<td>PostCA</td>
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<td>16 (13)</td>
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<tr>
<td>SMST</td>
<td>PostPU</td>
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<td>17 (9)</td>
<td>.95</td>
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<tr>
<td>NA</td>
<td>STR</td>
<td>15 (7)</td>
<td>16 (8)</td>
<td>.89</td>
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</table>

Abbreviations: See Table 3.

**IMPLICATIONS**

The findings of the present study challenge the idea that alternations of DA transmission in schizophrenia affect the mesolimbic rather than the nigrostriatal DA pathways. This hypothesis was formulated in the early 1970s45-49 notably in an influential article by Stevens.50 As pointed out by Lidsky,31 the striatum was conceptualized at that time as being mostly involved in motor control. The mesolimbic theory provided “conceptual relief” to the DA hypothesis of schizophrenia because the territories innervated by the mesolimbic DA system were known to be involved in modulation of drive, affect, and memory, dimensions more related to psychiatric symptoms than the motor functions ascribed to the striatum.

This widely held hypothesis also implied that blockade of D2 receptors in the VST was responsible for the antipsychotic effect, whereas blockade of these receptors in nigrostriatal pathways was associated only with undesirable motor side effects. This hypothesis led to the view that a “mesolimbic selectivity” was a desirable property in the development of new antipsychotic drugs. Indeed, at low doses, most “atypical” or “second-generation” antipsychotic drugs show a dose-related selectivity for affecting the firing of A10 vs A9 neurons and for inducing gene expression in the nucleus accumbens vs the corpus striatum.52-58

Nevertheless, it is not yet established whether the mesolimbic-selective effects of these drugs observed at low doses in animals are relevant at the doses used in clinical settings.59-62 Furthermore, the therapeutic superiority of “second-generation” antipsychotic drugs has recently been questioned by a number of clinical trials.63-65 An important consequence of this study is the proposition that the “mesolimbic” selectivity of second-generation antipsychotic drugs might not be relevant to their therapeutic effectiveness because the primary site of antipsychotic action related to D2 receptor blockade might be the AST. Regarding the LST, the study suggests that, if anything, low DA tone in the VST might be associated with severity of negative symptoms (passivity and social withdrawal). This observation is consistent with the role of limbic DA in reward66 and with the general lack of effectiveness of antipsychotic drugs on these symptoms.

It is now well established that the dorsal striatum, particularly the caudate nucleus, is involved in learning, habituation, memory, attention, motivation, emotion, and volitional behavior.67-70 Furthermore, the preDCA is the area of the striatum that receives the largest corticostriatal projections from the dorsolateral prefrontal cortex (DLPFC)71-73 (Figure 3), the neocortical area most implicated in the pathophysiologic mechanism of schizophrenia. The D2 receptors in the striatum modulate corticostriatal synapses onto medium spiny neurons and, therefore, the flow of information within corticostriatal loops.74-79 The human AST also receives convergent inputs from limbic-related cortical regions and therefore supports some integrative functions ascribed to the nucleus accumbens in rodents.80,81 Thus, the AST, particularly the preDCA, is in a unique position to integrate information from multiple regions and to regulate circuitry affecting DLPFC function. In schizophrenia, in-
Increased DA activity at D2 receptors in the AST might reduce the ability of the DLPFC to engage striatal processing functions because D2 receptor stimulation reduces glutamatergic transmission into striatal γ-aminobutyric acid–releasing medium spiny neurons.82 Subcortical DA dysregulation in schizophrenia has historically been conceptualized as a consequence of a primary DLPFC dysfunction.83,84 The results of this study suggest that alterations of subcortical DA transmission, if located in the preDCA, might in turn negatively affect DLPFC function. This proposition is directly supported by the recent observation that transgenic mice overexpressing D2 receptors selectively in the striatum exhibit selective cognitive impairments in working memory tasks and behavioral flexibility, behavioral competencies associated with prefrontal cortex.85

In conclusion, this study confirmed that DA occupies a higher proportion of striatal D2 receptors in patients with schizophrenia undergoing an episode of illness exacerbation than in matched controls. This increased DA transmission was localized to the associative regions of the striatum and, most specifically, the rostral and dorsal parts of the caudate, the regions of the striatum most involved in DLPFC information processing. These results, if replicated and extended, have important consequences for the understanding of the role of DA in schizophrenia and for the development of novel medications.

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