**Short report**

**Brain metabolism in patients with schizophrenia before and after acute neuroleptic administration**

**NORA D VOLKOW,**† **JONATHAN D BRODIE,** ALFRED P WOLF,† **BURT ANGRIST,**† **JEROME RUSSELL,**† **ROBERT CANCRO**†

*From the Department of Psychiatry, NYU Medical Center, and the Department of Chemistry, Brookhaven National Laboratories† and Department of Psychiatry, University of Texas in Houston, Houston, USA

**SUMMARY** Positron emission tomography (PET) with $^{11}$C-2-deoxyglucose ($^{11}$DG) was used to compare regional brain metabolism in four patients with chronic schizophrenia who had no history of psychotropic medication and in 12 normal controls. Patients had a second PET scan after an injection of thiothixene to evaluate the effects of acute neuroleptics on glucose metabolism. The patients showed higher glucose metabolic values than the normals and did not show the metabolic hypofrontality reported in chronic medicated patients with schizophrenia. Administration of the neuroleptic did not have a significant effect in the metabolic pattern of the patients. These results give support to the hypothesis that prolonged medication may contribute to the metabolic hypofrontal pattern seen in patients with schizophrenia.

Several studies using positron emission tomography (PET) report a decrease in glucose metabolism in the frontal cortex of patients with schizophrenia when compared with normals.1-3 These studies were conducted mainly in patients with a long history of psychiatric illness. Investigations on patients with a relatively short duration of illness have failed to show metabolic hypofrontality.4,5 On the other hand, abnormalities in basal ganglia metabolism have been described both in patients with acute and chronic schizophrenia.2,3,5 Neuroleptic treatment has been reported to accentuate the hypofrontal metabolic pattern4,4 and to increase the relative metabolic activity of the basal ganglia.

In this study $^{11}$C-2-deoxyglucose ($^{11}$DG) was used to compare glucose metabolism in patients with schizophrenia "naive" who have never been treated and in normal subjects. The hypothesis was that these patients would not show the metabolic hypofrontality seen in the chronic schizophrenia but would show basal ganglia dysfunction. This study also assessed the effects of acute neuroleptics administration on regional glucose cerebral metabolism of schizophrenic patients.

**Methods**

The experimental group consisted of four male subjects who fulfilled DSM III9 and RDC7 for schizophrenia ($\bar{x}$ = 28 years of age). Mean duration of illness was 8 years. Three of the subjects had never received neuroleptic treatment and the other had been treated with neuroleptics for three months, 12 months prior to the study. The control group consisted of twelve healthy male volunteers ($\bar{x}$ = 29 years of age). A complete medical and neurological examination was done on the controls and the patients to assure that there was no medical illness. All subjects were right-handed. The experimental procedure followed the ethical standards of the Committee for Protection of Human Subjects of New York University.

Subjects were tested with $^{11}$C-2-deoxyglucose ($^{11}$DG) and the PETT VI (FWHM 12 mm). Before the PET studies were initiated the sensitivity of the machine was tested using a Gallium 68 phantom ring. Once this was accomplished, the subject was positioned in the PET camera and a transmission image obtained using the same Gallium 68 ring. This image was then used to correct for attenuation. Brain glucose metabolism was assessed 40 minutes after venous bolus injection of 7–15 mCi of $^{11}$DG. During the procedure blood samples were obtained from an arterialised vein using a hand warmer device to monitor for radioactive plasma concentration. Blood samples were obtained at 20, 40, 60, and 90 seconds and at 2, 3, 4, 6, 8, 10, 15, 25, 30, and 45 minutes after injection.
Table  Regional glucose metabolism in normals and in schizophrenics before and after neuroleptic injection

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Normals (n = 12)</th>
<th>Schizophrenics (n = 4) before</th>
<th>Schizophrenics (n = 4) after neuroleptic injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Frontal</td>
<td>40.3 ± 3.0</td>
<td>45.9 ± 9.8</td>
<td>46.1 ± 7.7*</td>
</tr>
<tr>
<td>R. Frontal</td>
<td>40.0 ± 2.8</td>
<td>44.8 ± 9.3</td>
<td>45.0 ± 7.6</td>
</tr>
<tr>
<td>L. Parietal</td>
<td>39.0 ± 3.6</td>
<td>44.4 ± 7.7</td>
<td>45.4 ± 6.7*</td>
</tr>
<tr>
<td>R. Parietal</td>
<td>38.5 ± 2.7</td>
<td>44.2 ± 7.2*</td>
<td>44.3 ± 5.6*</td>
</tr>
<tr>
<td>L. Temporal</td>
<td>37.3 ± 3.1</td>
<td>43.4 ± 9.4</td>
<td>44.5 ± 8.4*</td>
</tr>
<tr>
<td>R. Temporal</td>
<td>37.5 ± 2.5</td>
<td>43.8 ± 9.5*</td>
<td>43.7 ± 7.7*</td>
</tr>
<tr>
<td>L. Occipital</td>
<td>43.2 ± 4.0</td>
<td>48.8 ± 9.2</td>
<td>48.5 ± 7.9</td>
</tr>
<tr>
<td>R. Occipital</td>
<td>44.1 ± 4.0</td>
<td>49.1 ± 9.3</td>
<td>48.9 ± 7.7</td>
</tr>
<tr>
<td>L. Basal ganglia</td>
<td>39.9 ± 3.4</td>
<td>47.1 ± 10.6*</td>
<td>47.5 ± 9.2*</td>
</tr>
<tr>
<td>R. Basal ganglia</td>
<td>38.1 ± 2.4</td>
<td>45.2 ± 9.7*</td>
<td>46.8 ± 9.0*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>37.9 ± 3.6</td>
<td>43.0 ± 10.1</td>
<td>43.6 ± 8.9</td>
</tr>
</tbody>
</table>

Comparisons refer to differences between the normals and the schizophrenics before and after 5 mg thiothixene. Values represent group means and SD for glucose metabolism (DG) expressed as mol/100 g/min.

L = left; R = right; * = p < 0.05; † = p < 0.005.

The images were transformed into metabolic images using Sokoloff's equation, a mean set of K values and a 0.49 value for the lumped constant. More details of the scan procedure and the calculation of regional glucose metabolic values utilised in this study have been reported.

The schizophrenic subjects had a second scanning procedure 60 minutes after they were injected with 5 mg IM of thiothixene. This scan was performed three hours after the first one.

Metabolic images were matched with the corresponding CT image from each subject for anatomical reference.

Regions of interest (ROI) were drawn by superimposing boundaries from a standard neuroanatomical atlas into the individual CT scan and then outlining corresponding regions in the metabolic images with a light pen on a video screen. Metabolic values for the gray matter of frontal, parietal, temporal and occipital lobes, basal ganglia and thalamus were obtained by matching corresponding regions from the different slices.

Cerebral metabolic rates before and after post acute thiothixene administration were analysed using a paired \( t \) test analysis. Cerebral metabolic rates for glucose were compared between the normals and the schizophrenics before neuroleptic injection, and after drug administration. Mean differences between the normals and the schizophrenics for the metabolic values of the regions of interest were tested for significance with two tailed Student's \( t \) test. In consideration of the "multiple comparison" problem, we adjusted the criterion of significance to \( p < 0.005 \). We selected an intermediate value between the \( p \) value considered significant in an individual variable \( p < 0.05 \) and the \( p \) value using a Bonferroni procedure \( p < 0.0038 \) since the Bonferroni procedure assumes that variables are independent whereas the metabolic variables are highly dependent with one another.

Results

The table shows the absolute metabolic values for the normal and the schizophrenic subjects before and after neuroleptic injection. Though not statistically significant the patients with schizophrenia showed overall higher regional metabolic values than the normal controls. This difference was accentuated after
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neuroleptic injection, and was statistically significant for the right basal ganglia.

The individual metabolic response to neuroleptic injection is shown in the figure. Three of the patients showed a slight global increase in metabolism while one of them showed a decrease in metabolism. The largest effects of neuroleptic on brain metabolism were at the level of the right basal ganglia. None of these changes reached statistical significance.

Discussion

We did not find metabolic hypofrontality in this group of patients with "naive" chronic schizophrenia. This finding is similar to the one reported by Sheppard and by Widen in a group of young patients with schizophrenia. These results differ, however, from those of PET studies with medicated chronic schizophrenic patients, which showed a decrease in metabolic activity of the frontal regions. It is not possible to draw firm conclusions from such a small sample. However, the results suggest that there may be an association between exposure to neuroleptics and the metabolic hypofrontality pattern.

These results also suggest the existence of at least two subgroups of schizophrenic patients in terms of absolute values in brain glucose metabolism: one with an overall decrease in glucose metabolism more marked for the frontal regions and another subgroup without hypofrontality and with normal or high metabolic activity. The latter appear to be younger and have had less exposure to psychotropic medication than the former.

The "naive" patients with schizophrenia showed increased metabolic activity in the basal ganglia, suggesting some functional abnormalities in the striatum in schizophrenia which exists before neuroleptic treatment and which may precede frontal abnormalities. The hypothesis that basal ganglionic dysfunction underlies the psychopathology in some cases of schizophrenia is not a new one and it has already been suggested that some of the antipsychotic properties of neuroleptic result from direct effects on the nigrostriatal system.

The acute administration of 5 mg of thiothixene did not appear to have a large effect on glucose consumption by the brain. Three of the subjects showed a slight increase in metabolic activity. The subject who showed a decrease in metabolism had been very anxious and agitated during the first scan and became calmer and more relaxed after the neuroleptic injection. None of the other three complained of sedation. More precise definition of the relations between the metabolic effects of neuroleptics and their behavioural effects will require a considerably larger subject sample.

Our results differed from the studies reported on the acute effect of neuroleptics in rats using autoradiographic techniques which showed decrease in absolute metabolic values of the cortical areas. This could be accounted for by differences in doses, in pharmacokinetics of the drugs, animal species and in region selection. With PET we are selecting large topographical areas so that localised regional changes are averaged out by partial volume effects.

The findings reported here, while preliminary and in need of further expansion, are important because of the rarity of "naive" patients with chronic schizophrenia. Future studies need to be designed to differentiate the effects of the natural evolution of the disorder from the effects of chronic psychotropic medication.

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