PET Studies of Glucose Metabolism in Patients with Schizophrenia

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The hypothesis of abnormal patterns of metabolism in schizophrenia was examined in a series of six young patients with psychotic symptoms satisfying the research diagnostic criteria. After intravenous injection of ^{11}C-glucose obtained through a photosynthetic process, the regional activity of ^{11}C in brain was measured with a four-ring positron camera. Regions of interest were obtained from computed tomographic images. Each patient underwent a second positron emission tomographic examinations after 4–5 weeks of treatment with a neuroleptic drug. No evidence of a hypofrontal pattern was found, but after treatment there was a reduced frontal uptake on the left side compared with temporal regions. The left-right asymmetry in the lentiform nucleus was reduced after treatment.

Earlier studies with regional cerebral blood flow technique [1, 2] suggest there may be differences in flow distribution between patients with schizophrenia and control subjects. Patients were reported to show lower blood flow in frontal regions, that is, hypofrontality, and this effect was considered to be related to their symptoms.

At a 1981 meeting on cerebral metabolism a few positron emission tomographic (PET) studies on the energy metabolic pattern in schizophrenia were reported, one of them from our group, supporting the results of the cerebral blood flow findings, that is, they showed a reduced energy metabolic rate in the frontal lobes relative to more posterior regions of the brain in comparison with the findings in control cases [3, 4].

In our previous study, eight schizophrenic patients were examined [4]. A one-ring PET image was then used for the measurements of regional glucose utilization. The ratio between the metabolic rate in the frontal and temporal cortex in the same tomographic slice was calculated for each schizophrenic patient and two control subjects. A statistically significant difference between the two groups was found—the schizophrenic patients having a lower ratio, though the difference was small. All those patients were on neuroleptic drugs at the time of examination, but were having manifest psychotic symptoms.

Subjects and Methods

Six schizophrenic patients were examined before and after treatment with neuroleptic drugs. They all satisfied the international research diagnostic criteria [5] and were all of the type 1 defined by Crow [6], also called "acute schizophrenia," and characterized by positive symptoms of delusions, hallucinations, and thought disorders. The mean age was 29 years and the duration of the disease varied from 6 months to 3 years, though there were relatively symptom-free intervals during those periods. In addition two healthy volunteers were examined.

Brain regions of interest were selected and marked with the aid of a cursor on displayed computed tomographic (CT) images of the same brain slice as the one examined with PET. Thirty cortical regions on each side were selected to correspond to functional (Brodman) areas in addition to centrally located structures. To allow accurate positioning in the CT and PET scans, a special head-positioning device was used [7]. This device enables repeat PET examinations of the same brain regions to be performed with great accuracy (fig. 1).

The tracer, ^{11}C-glucose, was prepared photosynthetically using green algae [8]. Chemical analysis with GLC and HPLC showed that the glucose was radiochemically pure. The radiochemical yield of pure glucose was about 25% based on the amount of $^{11}CO_2$ introduced to the algae. The preparation takes 35–40 min.

Between 3 and 5 mCi (111–185 MBq) of the tracer was injected intravenously and blood samples were repeatedly taken from the contralateral artery or heated arm vein. The content of unlabeled glucose as well as the activities of total ^{11}C and ^{11}C-CO_2 were determined.

A four-ring PET scanner was used, manufactured by the Scanditronix, Stockholm, and developed by members of our group [9]. In the present study no metabolic model for ^{11}C-glucose was applied. So far there exists no compartment model for PET studies with ^{11}C-glucose that gives satisfactory metabolic rates. However, in our previous study [4] we found a good correlation between the relative metabolic values obtained with a simple model and the relative net uptake of ^{11}C in different regions. In the present study we relate each time-averaged regional uptake of ^{11}C to the corre-

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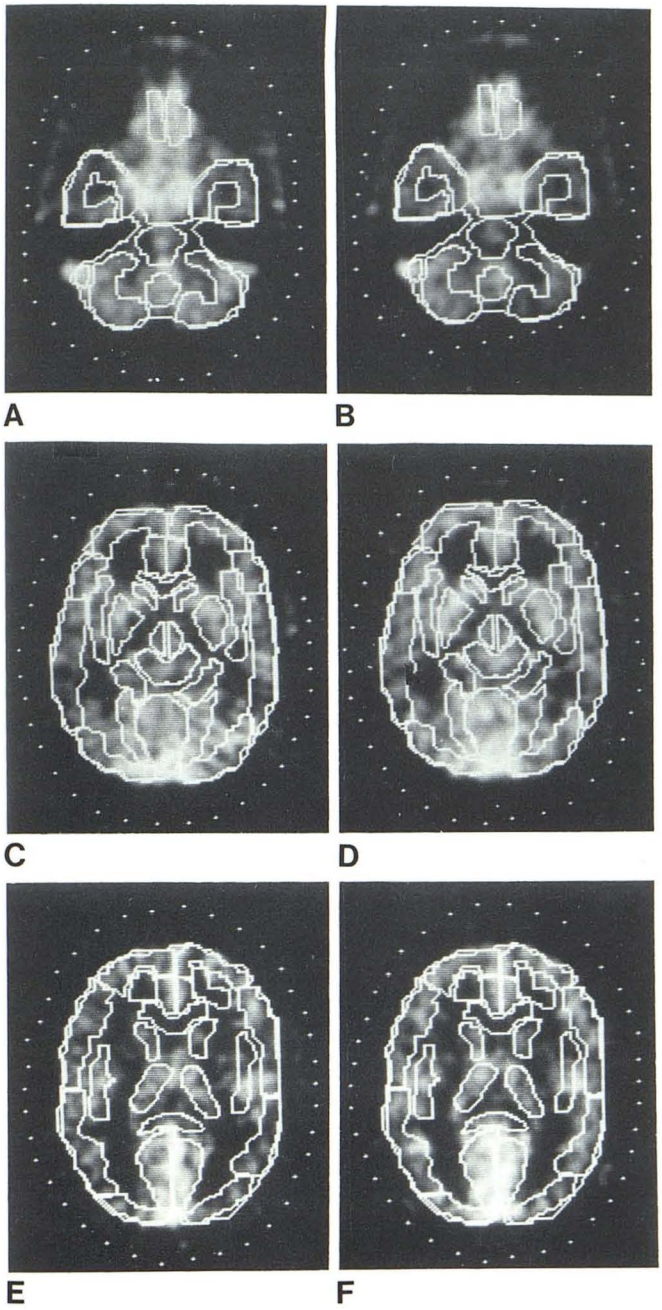

Fig. 1.—Regions of interest (ROIs) selected from CT and transferred onto PET images. The same areas are used twice, at first examination (**A**, **C**, and **E**) and after treatment with neuroleptic drugs (**B**, **D**, and **F**). Note reproducibility at patient alignment. Fixation system enables automatic transfer of ROIs from CT to PET and repeat use of ROIs.

sponding value for the total volume of the brain that can be covered with our camera without movement along the Z axis. For the average metabolic rate, however, we apply a model [4] that enables us to compare the effect of treatment for the brain as a whole.

Our patients underwent a second PET examination after 4–5 weeks of treatment with daily doses of a neuroleptic, a benzamide derivative, which is a DA antagonist. The plasma level of the drug was checked in each case.

TABLE 1: **Time-Averaged Net Uptake of ^{11}C in Nucleus Lentiformis**

Case No.	Right		Left	
	Before	After	Before	After
1	1.08	1.24	1.16	1.24
2	0.80	0.90	0.79	0.94
3	1.01	1.07	1.09	0.98
4	1.05	1.04	1.10	1.13
5	0.98	1.06	1.08	1.03
6	1.01	1.13	1.15	1.01
Mean	0.99	1.07	1.06	1.06
SEM	0.04	0.05	0.07	0.05

Note.—On the right side, the difference between mean values before and after treatment is significant on the 5% level (paired *t* test). Left-right asymmetry before treatment is also significant on the 5% level. No significant asymmetry after treatment.

TABLE 2: **Uptake Quotient between Premotor and Wernicke Areas (Brodman Areas 6, 8/39, 40)**

Case No.	Right		Left	
	Before	After	Before	After
1	1.08	1.05	1.04	1.00
2	1.04	1.00	1.16	0.98
3	1.07	1.08	1.12	1.10
4	1.13	1.01	1.14	1.03
5	1.04	0.99	1.11	0.96
6	0.99	1.05	1.10	1.05
Mean	1.06	1.03	1.11	1.02
SEM	0.02	0.02	0.02	0.02

Note.—On the left side, the difference between mean values before and after treatment is significant on the 5% level (paired *t* test).

Results

In our new material no obvious differences in metabolic pattern were found as compared with the controls. All patients had a lower relative uptake in the mesencephalon, but the difference was not significant on the 5% level in a two-sided paired *t* test.

There was no trend toward a reduced frontal/temporal metabolic ratio for the patients compared with the control cases. Furthermore, when the old and the new materials were put together there was no significant (at the 5% level) difference in this ratio, when measured in compatible tomographic brain slices, between the 14 patients and the four controls.

Certain morphologic [10, 11] and electrophysiologic differences [12] between the right and left hemispheres in schizophrenic patients as compared with control cases have been described. We compared the uptake quotients between right and left basal ganglia in our patients and found significantly higher uptake in the left lentiform nucleus (table 1).

After treatment with a neuroleptic drug, the uptake quotient between the premotor area (Brodman 6 and 8) and the Wernicke area (Brodman 39 and 40) decreased significantly in the left hemisphere (table 2), and there was a general tendency for the frontal/temporal uptake quotients to be reduced when the patients were on medication. They were still not hypofrontal but, possibly, had taken a small step toward hypofrontality. Furthermore, there was a reduction of the right-left asymmetry of the lentiform nucleus. The glucose uptake was significantly increased in the right lentiform nucleus after treatment causing the initial left-right asymmetry to disappear (table 1). Also the right caudate nucleus showed an increased net uptake after treatment in all cases, but this effect did not reach

TABLE 3: **Time-Averaged Net Uptakes on ^{11}C in Nucleus Caudatus**

Case No.	Right		Left	
	Before	After	Before	After
1	1.07	1.08	0.94	0.99
2	0.82	0.97	0.86	0.97
3	0.81	1.07	1.07	1.00
4	0.91	0.94	1.01	0.99
5	1.05	1.11	1.00	1.00
6	1.05	1.05	1.13	1.00
Mean	0.95	1.04	1.00	0.99
SEM	0.05	0.03	0.04	0.01

statistical significance (table 3).

Without our present sample, no evidence is found for a change in the overall metabolic rate after treatment.

Discussion

Our study population is still too small to allow definite conclusions. A tentative explanation of our findings is as follows: The differences between our previous and present findings may be explained by a different duration of the disease; our previous group comprised more chronic cases (half of the patients had a history of 10–20 years), whereas in the new group the symptoms were of more recent onset. This explanation is supported by the fact that the hypofrontality described in the previously mentioned cerebral blood flow studies as well as recent PET studies [13] was found mainly in patients with a long history, whereas in studies at Hammersmith (Frackowiak RSJ, personal communication) and the National Institutes of Health (Kessler R, personal communication) on schizophrenia of relatively short duration, hypofrontality was not demonstrated.

The hypofrontal pattern is thus found in patients with schizophrenia of long duration and with predominantly negative symptoms. Acute cases with positive symptoms do not show that pattern.

Neuroleptic drugs seem to reduce the frontal/temporal quotient as well as the left-right asymmetry. Prolonged medication may contribute to the development of the hypofrontal pattern. Our study population is small and our findings and conclusions preliminary, but they encourage us to continue our study of this tragic and enigmatic disease.

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