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Blood Flow and Oxidative Metabolism of the Brain in Patients with Schizophrenia

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Abstract. 55 patients with schizophrenia were divided into three groups according to the clinical symptoms: (1) productive schizophrenias, i.e. patients with hallucinations, catatonic excitation and stupor; (2) paranoia and schizophrenia simplex, and (3) non-productive schizophrenias, i.e. patients with schizophrenic defects and hebephrenia.

Total cerebral blood flow (CBF) and the rates of cerebral oxygen, carbon dioxide, glucose and lactate metabolism were investigated. Patients with productive schizophrenias displayed a significant increase in CBF (to an average of 101.4 ml/100 g min), CMR oxygen (to an average of 6.26 ml/100 g min) and CMR glucose (to an average of 12.11 mg/100 g min), i.e. CBF and CMR oxygen nearly doubled and CMR glucose more than doubled in comparison with normal findings. In patients with paranoia and schizophrenia simplex CBF and oxidative metabolism did not vary much and were within the normal range. Non-productive schizophrenias showed a significant decrease in CBF (to an average of 36.7 ml/100 g min), CMR oxygen (to an average of 2.20 ml/100 g min) and CMR glucose (to an average of 3.86 mg/100 g min) in comparison with both other groups of schizophrenias and the group of healthy young men.

The results demonstrated variations in CBF and oxidative metabolism of the brain in patients with distinct types of schizophrenia. It was possible to find a correlation between the mental state of the psychosis on the one hand and CBF and metabolism on the other. The high CBF and metabolic rates of the brain in productive schizophrenias might be due to disturbances in the cerebral metabolism of biogenic amines.

More than 100 years ago the German psychiatrist *Griesinger* (8) described insanity as a brain disease and *Meynert* (19) suggested some years later that hyperemia of the cerebral cortex provoked a state of agitation. However, the problem as to whether schizophrenia is due to pathobiochemical disturbances in the brain (2, 15, 22) or to psychogenic factors has not yet been solved. From the biological point of view, more emphasis has been placed on variations of bio-

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Dedicated to Prof. Dr. Dr. h.c. mult. *F. Linder* on the occasion of his 65th birthday.

genic amines or other transmitter substances (20, 21, 23) than to disorders in oxidative brain metabolism in schizophrenic reactions. Only a small number of measurements of cerebral blood flow (CBF), oxygen and glucose consumption of the brain in patients with schizophrenia have been performed, mostly about 20 years ago. These did not reveal any results differing from normal values (6, 7, 17, 24, 26).

It seemed unlikely to us that patients with severe mental disorders such as those present in schizophrenia would not show any variations in CBF and oxidative metabolism of the brain. We therefore studied CBF and metabolism in different types of schizophrenia to look for special variations of these biological parameters.

Material and Methods

Patients

The study was carried out in 55 schizophrenic patients who were in good physical health and aged from 17 to 56 (average 32 years of age) from the Department of Psychiatry, University of Heidelberg. From the clinical point of view, we divided the patients into three groups *before* the measurments began: (1) patients with 'productive' schizophrenias, i.e. patients in the acute state of schizophrenic psychosis with hallucinations, sensations of apprehension, catatonic excitation and catatonic stupor; (2) patients with paranoia or schizophrenia simplex, and (3) patients with 'non-productive' schizophrenias, i.e. patients with hebephrenia or schizophrenic defects.

All measurements were done before breakfast between 8 and 9 a.m. Most of the patients were not treated for some days before the day of measurement. Only patients with acute schizophrenic psychoses had to be given tranquilizing drugs, but the last dose was given the night before the measurements were performed, and which could be done without any marked difficulties even in patients with a productive schizophrenia.

Monitoring of arterial blood pressure by means of a sphygmomanometer over the arteria brachialis revealed normal values. All measurements dealt with here were carried out in normocapnia and normoxia. These parameters were respectively monitored either by $paCO_2$ and paO_2 with an Eschweiler apparatus or by CO_2 and O_2 content measured by gas chromatography (25). Patients with a $paCO_2$ outside the range of 35–43 mm Hg and an arterial CO_2 volume of 45–55 vol%, respectively, were not included in this study. Body temperature was measured in the axillae and hemoglobin concentration by means of a standard method (table I).

Analytical Techniques

CBF was measured by means of the *Kety and Schmidt* (16) technique as modified by *Bernsmeier and Siemons* (1). Concentrations of 21 vol% oxygen, 25 vol% nitrous oxide and 54 vol% nitrogen were used for the inspired gas mixture. Blood samples from the femoral artery and from the inferior bulb of the jugular vein were taken with motor syringes (1 ml/min). The concentrations of oxygen and CO_2 were determined by means of gas chromatography (25) and glucose and lactate concentrations by means of standard enzymatic methods both in arterial and mixed cerebral venous blood. The metabolic rates were calculated from the product of CBF and the corresponding arteriovenous differences.

Table I. Mean values ± SEM of hemoglobin, arterial blood pressure, body temperature and blood oxygen and carbon dioxide contents in 55 schizophrenic patients

Parameters	whole group n = 55	Productive schizophrenia n = 16	Paranoia and schizophrenia simplex n = 23	Non-productive schizophrenia n = 16
Hemoglobin, g %	14.3 ± 1.2	14.3 ± 1.0	14.5 ± 1.2	14.0 ± 1.6
Arterial blood pressure, mm Hg				
Systolic	118 ± 12	120 ± 23	118 ± 10	118 ± 10
Diastolic	76 ± 10	77 ± 16	76 ± 10	74 ± 8
Body temperature, °C	36.7 ± 0.8	36.8 ± 0.9	36.7 ± 0.8	36.6 ± 0.9
Arterial O_2, vol %	19.9 ± 1.1	19.9 ± 0.9	19.9 ± 1.1	19.5 ± 1.2
Arterial pO_2, mm Hg[1]	98 ± 7	99 ± 5	101 ± 8	96 ± 7
Arterial CO_2, vol %[1]	51.1 ± 5.2	50.8 ± 5.4	51.9 ± 4.8	50.1 ± 5.1
Arterial pCO_2, mm Hg	39 ± 4	40 ± 3	38 ± 4	39 ± 4

Statistically significant differences between the different groups of schizophrenic patients were not found.

[1] Arterial pO_2 and CO_2 were measured in only 32 patients (productive schizophrenia: 9; paranoia and schiophrenia simplex: 14, and non-productive schizophrenia: 9). In the remaining 23 patients, normoxia and normocapnia were related to the O_2 and CO_2 contents.

Statistical Methods

The mean values and standard deviations of hemoglobin, arterial blood pressure, body temperature, the blood oxygen and CO_2 volumes, paO_2 and $paCO_2$ were calculated by means of the t test. Differences in these data between the different groups of schizophrenia could not be found. We compared CBF, CMR oxygen, CMR CO_2, CMR glucose and CMR lactate for statistical differences by means of the analysis of variance for a one-way design. In another step, we calculated the medians and the non-quadratic deviations for CBF, CMR oxygen and CMR glucose. All values below the lower limit of the corresponding deviation or equal to this value were designated 'minus' and all values within the deviation 'zero'. All values above the upper limit of the deviation or equal to this value were designated 'plus'. Thus, 27 possible combinations (scores) between CBF, CMR oxygen and CMR glucose resulted from this statistical discrimination of the data. The mean values of the scores in each group and the statistical differences between the three mean values were calculated by means of analysis of variance for a one-way design. (For statistical advice and calculations we are indebted to Prof. *H. Immich*, Department of Medical Documentation and Statistics, University of Heidelberg.)

Ethical Considerations

This study is part of a program of clinical research on CBF and oxidative metabolism of the brain in more than 800 patients with different brain diseases, such as various forms of idiopathic dementia, post-traumatic head diseases, and alcoholism or liver cirrhosis, etc. One major stimulus to investigations of CBF and metabolism in schizophrenic patients was the theory of the German psychiatrist *Kurt Schneider* that schizophrenia is a psychosis whose

Table II. Mean values ± SEM of CBF and oxidative metabolism in 55 patients with different types of schizophrenia

Parameters	Productive schizophrenia n = 16	Paranoia and schizophrenia simplex n = 23	Non-productive schizophrenia n = 16	Controls n = 15
Age, years	32	31	34	25
CBF, ml/100 g min	101.4 ± 3.4	57.6 ± 2.8	36.7 ± 3.4	52.9 ± 4.9
Oxidative metabolism				
CMR Oxygen, ml/100 g min	6.26 ± 3.98	3.19 ± 3.31	2.20 ± 3.98	3.54 ± 0.42
CMR CO_2, ml/100 g min	6.01 ± 4.33	3.30 ± 3.61	2.20 ± 4.33	3.77 ± 0.51
CMR Glucose, mg/100 g min	12.11 ± 6.03	5.72 ± 5.03	3.86 ± 6.03	4.97 ± 0.75
CMR Lactate, mg/100 g min	1.60 ± 3.67	0.68 ± 3.06	0.54 ± 3.67	0.36 ± 0.22

The differences between each parameter in the three groups of patients are highly significant ($p \leq 0.01$).

underlying somatic origin is still unknown. Another important reason for measuring these biological parameters of the brain was to be able to base the diagnosis on reproducible 'hard' data. It was ethically justifiable to perform these measurements especially since the procedure is easy to perform and does not inconvenience the patients at all. All non-confused patients were informed of the aim of the investigation and permission to carry it out was obtained from them. In all cases with confusions or stupor, the closest relatives were informed and asked for permission to perform the measurements.

Results

The mean CBF and oxidative brain metabolism values which are listed in table II were significantly different ($p \leqslant 0.01$) from one group of schizophrenic patients to another. The median CBF of the three groups of schizophrenic patients was 60 ml/100 g min. The total range was from 175.0 to 17.6 ml/100 g min and the non-quadratic deviation from 40 to 80 ml/100 g min. The medians for CMR oxygen and CMR glucose were 3.08 and 6.35 mg/100 g min, respectively. The total ranges for CMR oxygen were from 12.67 to 0.83 ml/100 g min and for CMR glucose from 20.37 to 1.37 mg/100 g min and the non-quadratic deviations from 2.20 to 3.96 ml/100 g min and 2.96 to 9.74 mg/

Table III. Medians and non-quadratic deviations of CBF, CMR oxygen and CMR glucose based on 55 patients with different types of schizophrenias

	Median	Non-quadratic deviation
CBF, ml/100 g min	60	40–80
CMR oxygen, ml/100 g min	3.08	2.20–3.96
CMR glucose mg/100 g min	6.35	2.96–9.75

100 g min, respectively (table III). In patients with productive schizophrenias CBF was increased to an average of 101.4 ml/100 g min, i.e. to about 190 % in comparison with healthy young men (10). In the same group of patients, CMR oxygen was elevated to an average of 6.26 ml/100 g min, i.e. to about 180 % in comparison with normals and CMR CO_2 to 6.01 ml/100 g min, i.e. 159 %. The highest increase could be seen in CMR glucose which rose to an average of 12.11 mg/100 g min, i.e. 244 % as compared with the normal group. CMR lactate also increased markedly to 1.60 mg/100 g min and the lactate/glucose index went up from a normal value of 0.07 to 0.13 in productive schizophrenias. However, the increased lactate production only partly explains the elevated uptake of glucose into the brain. Thus, the increase in CMR glucose was in excess of that in CMR oxygen and an imbalance between CMR oxygen and the amount of oxidizable glucose existed. The mean values of CBF, CMR oxygen and CMR glucose in patients with the productive type of schizophrenia were also much higher than the medians and were outside the non-quadratic deviation for the whole collective of schizophrenic patients (table II, III).

Those patients who displayed paranoia or schizophrenia simplex did not show any larger variations in CBF and oxidative metabolism of the brain in comparison with either the corresponding values in normal young men or the medians and non-quadratic deviations of CBF, CMR oxygen and CMR glucose in all schizophrenic patients investigated in this study. However, all parameters measured here were significantly lower than in the group of productive schizophrenias. CBF was on average 57.6 ml/100 g min, i.e. about 110 % of normal values. CMR oxygen was 3.19 ml/100 g min and CMR CO_2 3.30 ml/100 g min, both about 90 % of normal values and CMR glucose was 5.72 mg/100 g min, i.e. about 115 % of normal values. The mean lactate/glucose index was elevated to 0.12.

In the group of patients with non-productive schizophrenias CBF was decreased to an average of 36.7 ml/100 g min, i.e. about 70 % of normal values. This value was also lower than the median and its non-quadratic deviation. CMR oxygen and CMR R CO_2 both dropped to 2.20 ml/100 g min, which was about 60 % of the normal values. In this group of patients, CMR oxygen was at the

Table IV. General synopsis on the scores (left side) and frequency within the groups of patients with different types of schizophrenia (right side)

Score	CBF	CMR oxygen	CMR glucose	Scores		
				non-productive schizophrenia	paranoia and schizophrenia simplex	productive schizophrenia
1	–	–	–	5	17	27
2	–	–	0	14	24	27
3	–	–	+	14	11	27
4	–	0	–	5	15	27
5	–	0	0	5	15	27
6	–	0	+	14	14	24
7	–	+	–	13	5	18
8	–	+	0	13	18	27
9	–	+	+	2	11	23
10	0	–	–	4	14	24
11	0	–	0	2	15	27
12	0	–	+	14	14	27
13	0	0	–	2	17	18
14	0	0	0	2	14	27
15	0	0	+	4	13	18
16	0	+	–	11	18	27
17	0	+	0		4	
18	0	+	+		14	
19	+	–	–		17	
20	+	–	0		14	
21	+	–	+		5	
22	+	0	–		17	
23	+	0	0		14	
24	+	0	+			
25	+	+	–			
26	+	+	0			
27	+	+	+			
Mean ± SEM				7.75 ± 1.22*	13.91 ± 1.02*	24.69 ± 1.22*
Confidence limits				5.15–10.35**	11.80–16.02**	22.09–27.29**

The differences between the mean values of the scores are statistically highly significant. * $p \leq 0.01$, ** $p \leq 0.001$.

lower limit of the non-quadratic deviation of the median. CMR glucose was decreased to an average of 3.86 mg/100 g min, i.e. about 80 % of the normal value, but was within the limits of the non-quadratic deviation of the median. The mean lactate/glucose index was 0.14. Compared with the corresponding

data in the two other groups of patients, CBF and oxidative metabolism of the brain were significantly decreased in patients with non-productive schizophrenias.

Table IV demonstrates the mean values, standard deviations and confidence limits of the scores which were based on the three parameters CBF, CMR oxygen and CMR glucose. Statistically high differences could be found between the mean values of the scores ($p \leqslant 0.01$) and between the confidence limits ($p \leqslant 0.001$) within the different groups of schizophrenic patients. Thus, not only CBF, oxygen consumption or glucose uptake of the brain was lower ($p \leqslant 0.01$) in the non-productive group and higher ($p \leqslant 0.01$) in the productive group as compared with the group of schizophrenic patients with paranoia or schizophrenia simplex and as compared to normal subjects. The findings also indicate that the scores which comprise these three parameters were lower ($p \leqslant 0.01$) in the patients with non-productive schizophrenias and higher ($p \leqslant 0.01$) in productive schizophrenias as compared with patients with paranoia and schizophrenia simplex, in whom intermediate scores dominated. The confidence limits of the scores within the different groups of schizophrenic patients did not overlap whereby the large statistical differences between the scores of the three types of schizophrenic patients were also demonstrated.

Discussion

The present findings on CBF and oxidative metabolism of the brain in patients with different types of schizophrenias indicated that some of them did show variations of CBF and cerebral oxidative metabolism. Thus, our results seem to be at variance with those of *Wilson et al.* (26), *Gordan et al.* (7), *Sokoloff et al.* (24) and *Della Porta et al.* (6) who could not find pathological changes of CBF and oxidative metabolism of the brain in patients with schizophrenia. However, all the investigators mentioned above did not differentiate between several types of schizophrenias. It might therefore be possible that only patients with paranoia and schizophrenia simplex and no patients with productive or non-productive schizophrenias had been investigated. If so, no changes in CBF and oxidative metabolism of the brain in comparison with healthy subjects were to be expected as shown by our results in patients with paranoia and schizophrenia simplex. Only *Kety et al.* (17) have classified their schizophrenic patients into catatonic, paranoid, hebephrenic and simple schizophrenias. However, their patients were obviously in chronic states of the psychosis (duration of the hospitalization from less than 1 year to 26 years) and were not in the acute psychotic phase of the disease as our patients with productive schizophrenia. This might explain why *Kety* and coworkers did not find any variations of CBF and CMR oxygen in schizophrenia as compared with normal results.

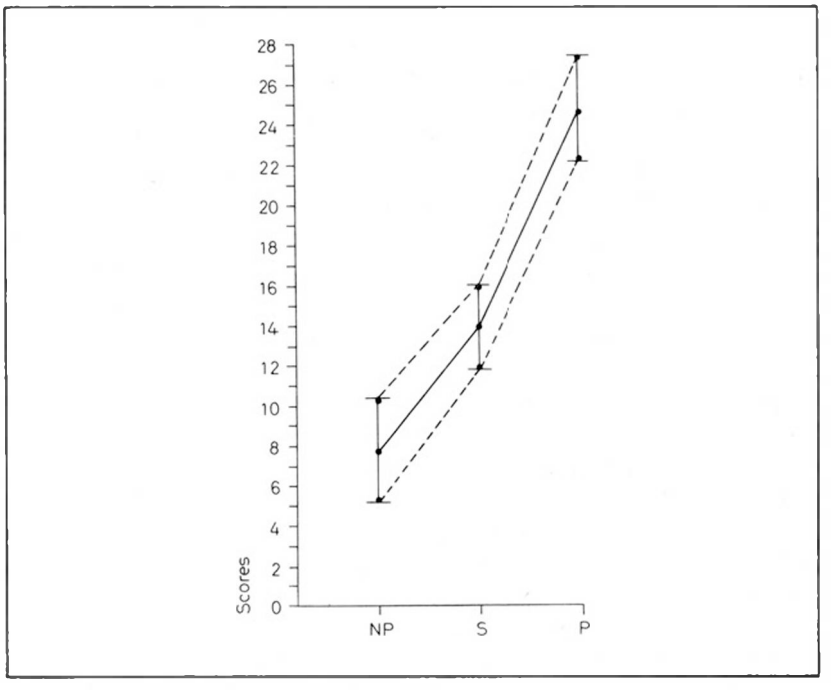

Fig. 1. Mean values of the scores comprising CBF, CMR oxygen and CMR glucose and confidence limits in patients with different types of schizophrenia. NP = Non-productive schizophrenia; S = paranoia and schizophrenia simplex; P = productive schizophrenia.

The present results demonstrated unequivocally that CBF and metabolism of the brain were significantly decreased in the non-productive type of schizophrenia. Thus, there existed a correlation between the biological parameters and the clinical symptoms of this group of patients. Furthermore, the changes in blood flow and oxidative metabolism of the brain in patients with non-productive schizophrenias demonstrated a striking similarity to variations of the same parameters in patients with dementia in whom brain functions were also decreased (11).

Productive schizophrenias comprising hallucinations, catatonic excitation and catatonic stupor were associated with significantly increased CBF and metabolic rates of the brain. All biological parameters were nearly doubled. In this type of schizophrenia a correlation between the clinical symptoms and the variations in total CBF and overall oxidative metabolism of the brain similarly occurred.

Thus, in general, a correlation between the clinical state of the psychosis on the one hand and the rate of CBF and metabolism of the brain on the other

seems to exist (fig. 1). A state of low mental and emotional activity was correlated with low CBF and oxidative metabolism of the brain, while sensations of apprehension, extreme anxiety and excitation were accompanied by a high CBF and high CMR oxygen, CMR glucose, CMR CO_2 and CMR lactate. These results are consistent with the findings of *Ingvar* (12) and *Ingvar and Franzen* (13) who demonstrated a strong correlation between the clinical state of the psychosis and changes in regional CBF in patients with chronic schizophrenia.

It is well established that under certain conditions CBF and CMR glucose nearly double (5, 9). However, the question is whether CMR oxygen can increase to a similar extent as CBF and CMR glucose. The present findings show clearly that CBF and the cerebral oxidative metabolism can increase to maximal rates in states of mental excitation. Thus, these results are in contrast to the assumption of an unchanged oxidative brain metabolism, especially CMR oxygen in various functional (pathological) mental states.

However, our data agree with *Kety*'s (14) who described an enhancement of CBF and CMR oxygen to values above normal in states of anxiety or apprehension. *King et al.* (18) and recently *Carlsson et al.* (3, 4) found marked elevations of CBF and CMR oxygen after l-epinephrine and amphetamine, respectively. The latter authors also reported significant increases in CBF and oxygen consumption of the brain in immobilization stress. They concluded 'that the increase in CMR oxygen represented a stress response mediated by adrenaline'. Based on these findings, one might speculate that at least in productive schizophrenias the elevations in CBF and oxidative metabolism of the brain are due to a pathological activation in the metabolism of biogenic amines in the brain.

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