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Chemistry, Physiology and Neuropsychology of Schizophrenia: Towards an Earlier Diagnosis of Schizophrenia I

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Summary. 1. Data supporting the glutamate hypothesis of schizophrenia are presented. The glutamate hypothesis is linked to the dopamine hypothesis by the fact that dopamine synapses inhibit the release of glutamate in the striate and mesolimbic system. The glutamate hypothesis of schizophrenia may open a way to find better drugs for treatment.

2. The concept of schizophrenia I is described. It consists of "negative symptoms" such as disconcentration or reduction of energy. Schizophrenia I precedes and follows schizophrenia II with "positive symptoms," e.g. hallucinations and delusions. Schizophrenia I so far cannot be diagnosed as schizophrenia unless schizophrenia II appears. Chemical, physiological or neuropsychological methods for the diagnosis of schizophrenia I would render an earlier treatment of schizophrenia possible and thus make social and occupational rehabilitation more efficient. An objective diagnosis of schizophrenia I may also elucidate the mode of genetic transmission of schizophrenia.

3. Several neuropsychological methods distinguish schizophrenic patients as a group from normals. Some of them are based on a specific disturbance of long term concentration.

4. The EEG also distinguishes schizophrenics from normals when analyzed during voluntary movement. For schizophrenics it takes more effort to initiate a voluntary movement, and there are several features of the EEG correlated to this. Moreover, the longer motor reaction time of schizophrenics is parallelled by a longer duration of the Bereitschaftspotential in schizophrenia. Furthermore, there is a difference in the theta rhythm between schizophrenic patients and normals in a task which requires concentration.

5. Some of the children of schizophrenic parents show a disturbance of concentration in both reaction time tasks and the d 2 test.

6. It is hoped that this line of research may lead to an earlier and more efficient treatment of schizophrenic patients. In the present situation most schizophrenic patients are treated too late and some of them are not helped at all.

Key words: Schizophrenia – Biochemical findings – Neurophysiology – Neuropsychology – Attention – Glutamate

Chemistry of Schizophrenia: the Glutamate Hypothesis

It is established beyond a reasonable doubt that schizophrenia has some genetic origin [5, 8, 31] and should, therefore, have some chemical basis. The search for psychotomimetic substances has so far been unsuccessful [16]. It is well documented, however, that neuroleptic drugs are effective in the treatment of schizophrenia, and the most likely mode of action of the neuroleptics is the blockade of the dopaminergic synapses [3, 33, 34, 36]. It has been hypothesized therefore that the primary cause of schizophrenia might be some disorder of the dopaminergic system. A hyperactivity of the dopaminergic endings could not be demonstrated, and consequently it was argued that there might be a hypersensitivity of the dopaminergic receptors in schizophrenia. This speculation, however, is not convincing in view of the fact that the hypersensitivity of dopaminergic receptors produced by long term neuroleptic treatment does not resemble schizophrenia.

Recently a new biochemical hypothesis of schizophrenia arose [20] from the finding that CSF glutamate is reduced in schizophrenic patients [18]. These results are not effects of neuroleptic drugs, since haloperidol even in high doses does not diminish the CSF glutamate level in the rat. Glutamic acid is probably the most important excitatory transmitter of the forebrain. Specifically, it is the transmitter of the cortico-striate and cortico-mesolimbic fibers [17].

The reduction of glutamic acid in the CSF of schizophrenic patients has recently been denied [29]; on closer consideration however, the author found the CSF glutamate in normal controls 40% higher than in schizophrenic patients. The small number of patients and the poor analytical method gave rise to the erroneous findings, and Perry admitted: "Our method ... is not sensitive enough for highly accurate measurement of the low concentrations of glutamate we find in human CSF." His figures were an order of magnitude lower than those of all other investigators [7, 9, 18, 38]. In another negative paper [6] the CSF was taken from patients in Brazil where it could not be stored at −80° C and than brought over to Germany for analysis, so that changes in the concentrations of glutamine and glutamate were likely to occur, especially since the concentration of glutamine is about ten times higher than that of glutamate. Thus the findings of Kim et al. [18] are probably still the best data available so far.

How may the therapeutic action of neuroleptic drugs be related to the glutamate findings? Dopamine blocks the release of glutamate in the striate [32]. The primary disturbance in schizophrenia might therefore consist of a hypoactivity of the glutamatergic neurons. Their cells of origin are in the cortex, and their fibers end in the striate and mesolimbic system. Thus blocking the inhibitory dopaminergic synapses by neuroleptics may result in enhanced release of glutamate.

Several experimental findings support this hypothesis: 1. Amphetamine enhances dopaminergic activity, and some amphetamine psychoses resemble schizophrenia. Chronic amphetamine treatment in the rat results in low CSF glutamate and in high brain glutamate in striate, hippocampus and frontal cortex [19]. 2. Neuroleptic drugs are expected to have the opposite effect: increase in CSF glutamate and reduction in brain tissue glutamate; this has been found in animal experiments with Sulpiride [21]. 3. Glutamate antagonists cause symptoms similar to schizophrenia. Glutamic acid diethylester induces catalepsy in

rats when injected into the lateral ventricle [25]. Phencyclidine and ketamine cause psychoses similar to schizophrenia in man; the horror trips following ketamine are well-known in anesthesiology. Phencyclidine is widely used as an hallucinogenic drug in America ("angel dust"). Both Phencyclidine and ketamine are probably antagonists of glutamate. 4. The axo-axonic synapses postulated by the glutamate theory of schizophrenia have been found morphologically in the striate [26]. – The influence of dopamine on the cortico-striatal and cortico-mesolimbic fibers may, however, also be mediated by gaba-ergic interneurons. We found a dose-dependent increase of the GABA level in the rat striatum under chronic haloperidol (submitted).

The glutamate hypothesis of schizophrenia may perhaps be of practical value in finding better drugs for the treatment of schizophrenic patients by searching for substances which abolish the action of glutamate antagonists. Such investigations may perhaps be possible in the peripheral neuromuscular system of invertebrates, since in the grasshopper and in the crayfish neuromuscular transmission is glutamatergic.

Schizophrenia I and II and Social Consequences

The psychosis with "positive" symptoms (hallucinations, delusions) is usually only a part of the course of schizophrenic illness. Before and after the positive symptoms there are stages of the disease characterized by negative symptoms such as disconcentration or reduction of psychic energy [13]. It is a finding of several detailed studies of schizophrenia that in retrospect the defect symptoms (appearing after the end of the first acute psychosis) did in fact precede the onset of that psychosis as prodromal symptoms [2, 13]. Since the disease with the negative symptoms comes first, it has been called schizophrenia I, while the psychosis with positive symptoms was termed schizophrenia II [22]. Unfortunately, the uncharacteristic symptoms of schizophrenia I cannot be diagnosed so far as schizophrenia unless schizophrenia II appears. This is the reason why schizophrenia is usually diagnosed and treated so late that the social relations of the patient have already been seriously disturbed by the disease. Social and occupational rehabilitation in schizophrenia would be easier if the diagnosis could be made at the stage of schizophrenia I.

Furthermore, there are probably many patients who have only schizophrenia I and never schizophrenia II. When schizophrenia starts in childhood, the clinical picture usually resembles schizophrenia I and is therefore often misdiagnosed as low grade mental deficiency. In the families of schizophrenic patients low grade mental deficiency is above average [10, 11]. It has been suspected by researchers who elucidated the course of schizophrenia that "latent schizophrenia" may be the most common, but undiagnosed form of schizophrenia [13]. Many of the undiagnosed patients are probably in casual wards and prisons instead of being successfully treated.

For these and similar reasons we need methods for the objective diagnosis of schizophrenia I from chemical, physiological or neuropsychological data. Such methods may also elucidate the discussion of the mode of genetic transmission of schizophrenia which so far is based on the diagnosis of schizophrenia II [8].

Neuropsychological and Physiological Methods for the Diagnosis of Schizophrenia I

A disturbance of the smooth pursuit eye movements in schizophrenic patients has been described [12]. Reinvestigating it we found this disturbance so small that it was not useful as a diagnostic tool. The saccadic eye movements, however, to a random stimulus program showed consistently increased latencies, nonfixation and dysmetria [1, 32a]. A comparison with depressed patients showed that dysmetria is characteristic for schizophrenia and does not occur in depression. The disturbance of saccadic eye movements in schizophrenic patients is not due to neuroleptic treatment as was confirmed by control experiments. In these patients the saccadic disturbance is obviously not a motor problem since normal saccades are sometimes seen between disturbed saccades. Obviously the disturbance is due to the impairment of concentration which is a basic sign of schizophrenia I.

It is an old finding that the simple reaction time in schizophrenics is longer than in normal controls. Furthermore, while normals can shorten their reaction time over a waiting period of approximately 20 s if a warning stimulus precedes the indicative stimulus by a fixed time, schizophrenic patients can do so only for 3 s; thereafter, their reaction time is even longer than without warning [35]. This cross-over phenomenon is specific for schizophrenia [30]. Combining the simple reaction time with the cross-over data from experiments with warning stimuli we could empirically define a score which distinguishes all our schizophrenic patients so far investigated from the normal controls adjusted for age and intelligence [14].

Since the investigation should be extended to the children of schizophrenic patients, normal children were investigated for comparison [24]. The younger the child, the longer is the simple reaction time in normal children. However, normal children are able to shorten their reaction time over the same period (about 20 s) as adults when a warning stimulus is given with a fixed interval before the indicative stimulus. The cross-over phenomenon of schizophrenic patients indicates that schizophrenics can concentrate for only 2 s. After that, the intention to concentrate increases their reaction time even more. This cross-over phenomenon does not occur in normal children.

A significant difference between schizophrenic patients and normal controls (adjusted for age, sex and intelligence) was also found with random button pushing. In this test [28] a number of buttons arranged irregularly on a plate have to be pressed in random order. Using the statistics of information theory, entropy is calculated as a measure of randomness. This test also divides the schizophrenic patients from the normal controls significantly. The schizophrenics are obviously unable to concentrate over a longer time, to memorize the order of button pressing or to generate a random motion pattern [14].

EEG Diagnosis of Schizophrenia

Until recently attempts to find EEG signs of schizophrenia were unsuccessful. The occurrence of slow (delta) waves in the EEG of schizophrenic patients is probably a nonspecific correlate of the inability to maintain a steady level of alertness. We could not confirm that schizophrenic patients have increased beta

power density [15]; perhaps the American finding was due to tranquillizers. However, when comparing the EEG at rest with the EEG in the Bereitschaftspotential [23] period before a voluntary movement and during the voluntary movement, six EEG signs of schizophrenia were observed [39, 40]. For these investigations a new method of EEG analysis was developed which allows analysis of the frequency content from EEG segments of 1 s duration [4].

In normal controls there is little change in the alpha rhythm during simple finger movements. In schizophrenic patients however, the alpha central frequency increases significantly from the Bereitschaftspotential period (1 s before the movement onset in the EMG) to the movement period. This corresponds to the fact that for schizophrenics it takes more effort to initiate a voluntary movement. Similarly, the alpha power density is more reduced in schizophrenic patients from rest to movement over the motor and parietal cortex than in normal controls. Untreated acute schizophrenic patients have less surface negative shift during the Bereitschaftspotential than normals. In well treated schizophrenics the Bereitschaftspotential lasts twice as long as in normal controls of the same age and intelligence (1.5 vs 0.8 s). This corresponds to the fact that the schizophrenics have a longer motor reaction time. Despite the long rise of the Bereitschaftspotential, however, the amplitude is small in schizophrenia. In central and parietal leads during rest schizophrenic patients have significantly more theta power density than normals. In normals the alpha central frequency is significantly slower over the motor and supplementary motor areas than over the parietal cortex. This difference is significantly diminished in schizophrenic patients [39, 40]. Furthermore, there are significant differences in the theta rhythm which is of limbic origin and shows maximum amplitude over the midline of the forebrain. The theta rhythm becomes slower and larger in reaction time experiments with warning stimuli. In such experiments the theta rhythm is faster in schizophrenic patients than in normals (Foit, Grözinger, Kornhuber et al. unpublished).

Children of Schizophrenic Patients

In view of the specific schizophrenic disturbance of long term concentration, research workers should not be demotivated by the negative findings of studies with nonspecific hypotheses such as lability of the autonomic nervous system as basis for vulnerability to schizophrenia [27]. So far we can distinguish schizophrenic patients as a group significantly from the group of normal controls. Whether the methods are good enough to make the diagnosis in the single case is a task for further investigation.

Furthermore, we can now present data from an investigation of 18 children of schizophrenic parents; this study has been carried out in collaboration with Dr. Gisela Stolz. As stated above, normal children are able to shorten their reaction time over about the same period as adults when a warning stimulus is given with a fixed interval before the indicative stimulus. A substantial number of the children of schizophrenic parents however, behave similarly to adult schizophrenic patients; therefore, all 18 children of schizophrenic patients taken together can shorten their reaction time only for approximately 5 s, and after that there is a pathologic cross-over phenomenon as in schizophrenic

patients. This disturbance of concentration in the reaction time task in some children of schizophrenic patients is correlated with a disturbance of concentration as measured by the d 2 test of Brickenkamp in the same children. These preliminary data from 18 children encourage us to continue this long term research which may, as we hope, ultimately lead to an earlier diagnosis and more efficient treatment and rehabilitation of the schizophrenic patients, avoiding long hospitalisations and using the traditional family and occupational feedbacks in addition to pharmacotherapy.

References

1. Becker W, Diekmann V, Kornhuber HH, Schmid-Burgk W (1982) Schizophrenie: sakkadische Augenbewegungen gestört. Dtsch Med Wochenschr 107 : 556
2. Chapman J (1966) The early symptoms of schizophrenia. Br J Psychiatr 112 : 225–251
3. Creese I, Burt DR, Snyder SH (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of anti-schizophrenic drugs. Science 192 : 481–483
4. Diekmann V, Foit A, Grözinger B, Kornhuber HH (1982) Spectral EEG changes during preparation, performance and evaluation of aimed hand-arm-movement: maximal alpha-depression over mesial cortex during movement. 1st World Congr IBRO Neuroscience, Suppl to vol 7, p 54
5. Fieve RR, Rosenthal D, Brill H (eds) (1975) Genetic research in psychiatry. Johns Hopkins University Press, Baltimore
6. Gattaz WF, Gattaz D, Beckmann H (1982) Glutamate in schizophrenics and healthy controls. Arch Psychiatr Nervenkr 231 : 221–225
7. Gjessing LR, Gjesdahl P, Sjaastad O (1972) The free amino acids in human cerebrospinal fluid. J Neurochem 19 : 1807–1808
8. Gottesman II, Shields J (1982) Schizophrenia: The epigenetic puzzle. Cambridge University Press, Cambridge
9. Grünert A, Schmid H (1983) Die präoperativen Aminosäurenkonzentrationen des stoffwechselgesunden Erwachsenen im Plasma und Liquor unter definierten präoperativen Bedingungen. Infusionstherapie (in press)
10. Hallgren B, Sjögren B (1959) The clinical and geneto-statistical study of schizophrenia and low-grade mental deficiency in a large Swedish rural population. Acta Psychiatr Neurol Scand [Suppl] 140 : 1
11. Heston LL (1966) Psychiatric disorders in foster home reared children of schizophrenic mothers. Br J Psychiatr 112 : 819–826
12. Holzman PS, Proctor LR, Levy GL, Yasillo NJ, Meltzer HY, Hurt SW (1974) Eye-tracking dysfunctions in schizophrenic patients and their relatives. Arch Gen Psychiatr 31 : 143–151
13. Huber G, Gross G, Schüttler R (1979) Schizophrenie. Eine verlaufs- und sozialpsychiatrische Langzeitstudie. Springer, Berlin Heidelberg New York
14. Hufnagl M, Kornhuber HH (1984) Quantitative Messung der Aufmerksamkeitsstörung von Schizophrenen durch Random-Zeigeversuch und Reaktionszeiten (in press)
15. Itil TM (1980) Computer-analysed electroencephalogram to predict the therapeutic outcome in schizophrenia. In: Baxter C, Melnechuk T (eds) Prospectives in schizophrenia research. Raven Press, New York, pp 61–75
16. Iversen LL (1978) Biochemical and pharmacological studies: the dopamine hypothesis. In: Wing JK (ed) Schizophrenia, towards a new synthesis. Academic Press, London; Grune and Stratton, New York, pp 89–116
17. Kim JS, Hassler R, Haug GP, Paik KS (1977) Effect of frontal ablations on striatal glutamic acid level in rat. Brain Res 132 : 370–374
18. Kim JS, Kornhuber HH, Schmid-Burgk W, Holzmüller B (1980) Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. Neurosci Lett 20 : 379–382

19. Kim JS, Kornhuber HH, Brand U, Menge HG (1981) Effects of chronic amphetamine treatment on the glutamate concentration in cerebrospinal fluid and brain: Implications for a theory of schizophrenia. Neurosci Lett 24 : 93–96
20. Kim JS, Kornhuber HH (1982) The glutamate theory in schizophrenia: clinical and experimental evidence. In: Namba M, Kaiya H (eds) Psychobiology of schizophrenia. Pergamon Press, Oxford New York, pp 221–234
21. Kim JS, Claus D, Kornhuber HH (1983) Cerebral glutamate, neuroleptic drugs and schizophrenia: increase of cerebrospinal fluid glutamate and decrease of striate glutamate following sulpiride treatment in rats. Eur Neurol (in press)
22. Kornhuber HH (1983) Biochemie, Physiologie und Neuropsychologie der Schizophrenie. In: Gross G, Schüttler R (eds) Empirische Forschung in der Psychiatrie. Schattauer, Stuttgart New York, pp 93–105
23. Kornhuber HH, Deecke L (1965) Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. Pflügers Arch 284 : 1–17
24. Kornhuber HH, Deecke L, Diekmann V, Grözinger B, Hufnagl M, Kornhuber M, Lang M, Lang W, Neher KD, Reinke W, Westphal KP (1982) Bereitschaftspotential, directed attention potential and related potentials: children, attention and schizophrenia. In: Rothenberger A (ed) Event-related potentials in children. Elsevier Biomedical Press, Amsterdam, pp 231–242
25. Kornhuber J, Fischer EG (1982) Glutamic acid and diethylester induces catalepsy in rats. A new model for schizophrenia? Neurosci Lett 34 : 325–329
26. Kornhuber JJ, Kornhuber ME (1983) Axo-axonic synapses in the rat striatum. Europ Neurol (in press)
27. Mednick SA, Schulsinger F (1973) Studies of children at high risk for schizophrenia. In: Dean SR (ed) Schizophrenia. The first ten Dean Award Lectures. MSS Information Corporation, New York, pp 247–293
28. Mittenecker E (1960) Die informationstheoretische Auswertung des Zeigeversuchs bei Psychotikern und Neurotikern. Z Exp Angew Psychol 7 : 392–400
29. Perry TL (1982) Normal cerebrospinal fluid and brain glutamate levels in schizophrenia do not support the hypothesis of glutamatergic neuronal dysfunction. Neurosci Lett 28 : 81–85
30. Pfeiffer K, Maltzman J (1976) Warned reaction times of manic-depressive patients with and without Lithium. J Abnorm Psychol 85 : 194–200
31. Rosenthal D, Kety SS (eds) (1968) The transmission of schizophrenia. Pergamon Press, Oxford
32. Rowlands GJ, Roberts PJ (1980) Activation of dopamine receptors inhibits calcium-dependent glutamate release from cortico-striatal terminals in vitro. Eur J Pharmacol 62 : 241–242
32a. Schmid-Burgk W, Becker W, Diekmann V, Jürgens R, Kornhuber HH (1982) Disturbed smooth pursuit and saccadic eye movements in schizophrenia. Arch Psychiatr Nervenkr 232 : 381–389
33. Seeman P, Chau-Wong M, Tedesco J, Wong K (1975) Brain receptors for anti-psychotic drugs and dopamine: direct binding assays. Proc Natl Acad Sci USA 72 : 4376–4380
34. Seeman P, Lee T, Chau-Wong M, Wong K (1976) Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 261 : 717–719
35. Shakow D (1963) Psychological deficit in schizophrenia. Behav Sci 8 : 275–305
36. Snyder SH, Creese I, Burt DR (1975) The Brain's Dopamine receptor: Labelling with ^{3}H-Dopamine and ^{3}H-Haloperidol. Psychopharmacol Commun 1 : 663–673
37. Timsit M (1970) Étude du phenomène de Kornhuber chez les schizophrenes et les cas limitées. Rev Neurol 122 : 449–451
38. Van Sande M, Mardens Y, Adriaenssen K, Lowenthal A (1970) The free amino acids in human cerebrospinal fluid. J Neurochem 17 : 125–135
39. Westphal KP, Neher KD, Grözinger B, Diekmann V, Kornhuber HH (1983) Zwei EEG-Symptome der Schizophrenie. Dtsch Med Wochenschr 108 : 117

40. Westphal KP, Neher KD, Grözinger B, Diekmann V, Kornhuber HH (1983) Six EEG-signs of schizophrenia. 7th Internat Conf on Event-related Potentials of the Brain. EPIC VII, Florence

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Note Added in Proof

There is supporting indirect evidence from a post mortem investigation of the brains of schizophrenic patients for a possible role of Glutamatergic transmission in the etiology of schizophrenia in the recent paper of T. Nishikawa et al., Neurosci Lett 40 : 245–250, 1983