Pathophysiologic Mechanisms in the Pathogenesis and Clinical Course of Schizophrenia

Jeffrey A. Lieberman, M.D.

It is widely accepted that schizophrenia originates from abnormalities occurring during the early stages of neural development. Although large studies have revealed behavioral precursors of schizophrenia in childhood, the disorder is usually not evident until patients are in their 20s or 30s. Some patients will be resistant to typical antipsychotic treatment at this first-onset of schizophrenia; however, treatment resistance develops in the majority of patients during the course of successive episodes. This ongoing deterioration suggests that a degenerative process operates during the active psychotic phase of the illness. This review presents evidence of neurodevelopmental and neurodegenerative mechanisms for the development of schizophrenia. These data indicate the importance of effective treatment at the first onset of schizophrenia to improve patient outcome. In addition, animal studies suggest that treatment with clozapine may prevent the neurodegenerative component responsible for the development of treatment resistance. *(J Clin Psychiatry 1999;60[suppl 12]:9–12)*

Schizophrenia typically develops in the early 20s in men and the late 20s to early 30s in women. A minority of patients are resistant to treatment with typical antipsychotics at onset; however, many patients become treatment resistant during subsequent episodes of the illness. Risk factors include a family history of schizophrenia and a fetal history of obstetric complications. This clinical course of schizophrenia and the identified risk factors have led to the belief that the diathesis occurs neurodevelopmentally during gestation from a combination of pathogenic factors and has a period of dormancy before the onset of symptoms. Nevertheless, some patients also seem to have the capacity for further limited neurodegeneration, which is presumably distinct from the neurodevelopmental diathesis that precedes it. This article reviews some of the evidence of a neurodevelopmental and a neurodegenerative mechanism in the development of schizophrenia. The therapeutic strategies for preventing these 2 forms of treatment resistance may need to be different, but research on the animal model suggests that pharmacologic treatment with atypical antipsychotic drugs may prevent the pathophysiologic process responsible for the neuroprogressive aspect of the illness.

From the Department of Psychiatry and Mental Health and Neuroscience Clinical Research Center, University of North Carolina School of Medicine, Chapel Hill.

Presented at the meeting "Treatment-Resistant Schizophrenia and Beyond: Current Concepts and Future Prospects," June 8–9, 1998, London, U.K. This meeting was supported by an educational grant from Novartis Pharma AG.

Reprint requests to: Jeffrey A. Lieberman, M.D., Department of Psychiatry and Mental Health and Neuroscience Clinical Research Center, University of North Carolina School of Medicine CB7160, 7025 Neurosciences Hospital, Chapel Hill, NC 27599-7160.

THE DEVELOPMENT OF TREATMENT RESISTANCE

It is widely acknowledged (though not as yet proven) that schizophrenia originates from a disturbance in the earliest stages of neural development, during gestation and the early postnatal period. During this time, the nervous system is proliferating, differentiating, migrating to target locations, establishing synaptic connections, and producing refinements in viable cell populations and circuits that will be sustained into adult life. However, these neurodevelopmental abnormalities usually remain dormant during childhood and adolescence. Although some behavioral precursors, such as disordered motor development, have been identified in children who later develop schizophrenia,[1] these differences are generally not severe enough or sufficiently specific to identify an individual patient before the onset of the illness.

Schizophrenia may have its origins in neurodevelopmental pathology, but only a small proportion of patients (10%–15%) are treatment resistant at the onset of the illness.[2] However, between 30% and 60% of patients with schizophrenia eventually become treatment resistant or only partially responsive to treatment. Therefore, many patients seem to develop either the capacity to be unresponsive to treatment or a more severe form of the illness that no longer responds to treatment. These observations imply that there are 2 pathogenic processes for schizophrenia, a developmental process and a limited neurodegenerative process that underlies the progressive phase of the illness.

An understanding of the relationship between the clinical course of schizophrenia, including the development of treatment resistance, and the underlying pathophysiology may reveal opportunities for therapeutic intervention to prevent the development of schizophrenia and of treatment resistance in patients who have already developed the disorder.

EVIDENCE OF A NEURODEVELOPMENTAL MECHANISM

A variety of etiologic factors have been suggested for schizophrenia. These include a genetic defect, an infection or immune response transmitted from the mother to the fetus across the placenta, and obstetric complications. All of these factors may affect the generation of nerve growth factors and their ability to stimulate viable cell development, by the stimulation of cytokines, infection, hypoxia, trauma, or stress-induced neurochemical effects. Thus, disturbances of processes involving neurotrophic factors during development may explain the underlying pathology of schizophrenia.[3]

A study of pregnant women who had been exposed to infection or physical trauma or were schizophrenic revealed an inverse relationship between gestational age and amniotic fluid levels of 3 different forms of nerve growth factors, brain-derived neurotropic factor (BDNF), neurotrophin-3 (NT-3), and nerve growth factor (NGF).[4] Lower concentrations of nerve growth factors, particularly NGF, were evident in fetuses who had central nervous system (CNS) abnormalities or had been exposed to infection. Thus, NGF could be a marker for the process that results in limited or disrupted neural development in fetuses who develop schizophrenia in later life.

Imaging studies have identified abnormal brain morphology in schizophrenic patients. Studies using in utero ultrasonography have demonstrated that the lateral ventricles of some fetuses are enlarged as early as the third trimester of gestation and remain enlarged postnatally when examined in childhood with magnetic resonance imaging (MRI) (J. H. Gilmore, J. van Tol, H. Lewis-Streicher, et al., manuscript submitted.) This suggests that ventricular enlargement is a hallmark pathomorphologic feature of adult schizophrenia and can be detected in individuals long before the formal onset of the illness and as early as in utero. A comparison of patients who have first-episode schizophrenia with healthy controls also demonstrated that the ventricular volumes of the patients with schizophrenia were significantly larger, with significantly larger temporal horns than those of controls.[5] In addition, the patients with first-episode schizophrenia showed relative reductions in left hippocampal volume compared with control subjects. Interestingly, first-episode patients with no ventricular enlargement are more responsive to treatment and have a faster rate of response.[2]

Studies conducted by Owen and colleagues have indicated an association between ventricular enlargement and obstetric complications.[6] Patients whose birth was accompanied by severe obstetrical complications had a ventricular volume of 22 cc compared with 16.7 cc in patients with no history of severe obstetrical complications.[7] This suggests that the enlargement of the ventricles is a consequence of the same phenomena that influence the likelihood to experience obstetric complications. In addition, patients with a history of severe obstetrical complications have a poorer treatment outcome, duration, and level of remission than patients without a history of such complications.[7] Thus, enlarged ventricular volume and obstetrical complications may define a neurodevelopmental form of schizophrenia which comprises a phenotype that manifests poor outcome and poor response to conventional antipsychotic drug treatment.

EVIDENCE OF A NEURODEGENERATIVE PROCESS

The development of treatment resistance during successive episodes of illness suggests that schizophrenia has a progressive pathophysiologic component during the active psychotic phase of the illness that engenders treatment resistance. This is particularly evident in the early phase of the illness, the prodromal phase, and the 5 years immediately after the first episode of the illness.[8] The time to remission increases in each successive psychotic relapse. In one study, mean group time to remission increased by 10 days in the second episode, and for those patients who had 3 episodes, there was a further substantial increase in time to remission.[9] Thus, patients may be slightly less responsive to treatment during successive episodes or exacerbations, such that some residual symptoms remain as well as decrements in the patients' functional capacity. Furthermore, first-episode patients with a longer duration of symptoms have lower and slower rates of remission than those with a shorter duration of symptoms, providing further support of a neurodegenerative process during the active psychotic phase of the illness.[10,11] These studies indicate that patients should receive early effective intervention to prevent treatment resistance.

Neuroimaging studies have provided evidence of a neuropathologic basis of the development of treatment resistance. First-episode patients, who were largely treatment naive, were followed by MRI at baseline and 3 years later (reference 9 and J. H. Gilmore, J. van Tol, H. Lewis-Streicher, et al., manuscript submitted). There was no difference in change in ventricular volume between schizophrenic patients and healthy volunteers. However, if the patients were grouped by outcome, the good outcome patients (those who remitted and did not relapse) had a lower initial ventricular volume than those with a poor outcome (patients who did not remit or remitted but relapsed) and

showed no change in ventricular volume, whereas those with a poor outcome showed a significant increase in ventricular volume. Similar changes were also observed in cortical volume. Since these preliminary data were reported, 3 other groups have found similar results, all in young or first-episode patients.[12–14] For example, Rapoport et al.[14] found that the ventricular volume of a sample of patients with childhood-onset schizophrenia significantly increased between the baseline and 2-year follow-up, whereas there was no change in healthy controls. Similarly, patients with abnormal brain morphology, particularly of the lateral and third ventricles, take longer to reach remission.[11]

Candidate theories for the potential neurodegenerative pathophysiologic processes involve dopamine projections to the cortex[15] and glutamate projections from the cortex to subcortical structures, as evidenced by the psychotogenic effects of glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonists.[16] The synaptic regulation of dopamine is known to be impaired in patients with schizophrenia; therefore, an animal model of synapsin-knockout mice has recently been used to try to further understand this pathophysiology of schizophrenia.

Synapsins are a family of neuron-specific proteins that have been implicated in the development of synapses and neurotransmitter release. Three distinct genes for synapsin I, II, and III have been identified, each of which has been implicated in the pathophysiology of schizophrenia. Synapsin IA, IB, and synaptophysin mRNA levels in the temporal gyri correlated negatively and significantly with age, whereas no such relationship was observed in normal controls.[17] Synapsin II variants have been identified in 56% of postmortem brain samples from individuals with schizophrenia compared with 31% of samples from nondiseased individuals, although patient numbers were low and this difference was not statistically significant.[18] In addition, the gene for synapsin III is located at a possible schizophrenia susceptibility locus, on chromosome 22q12-13.[19]

Knockout mice for synapsin I, II, or both have been used to examine the role of synapsins in neurodevelopment and neurotransmission. Mice with 2 or more mutant alleles for synapsins I and II have no gross abnormalities, but have seizures with a frequency proportional to the number of mutant alleles.[20] The number of synaptic vesicles are reduced to about 50% in mutant synapses of double-knockout mice compared with wild-type synapses. The functional significance of this is a diminished release of neurotransmitters, including GABA and glutamate, upon repeated stimulation in synapsin II and double knockouts, but not synapsin I knockouts. Therefore, in patients with schizophrenia, there may be a deficiency in GABA-mediated inhibitory effects in the cortex or glutamate hypofunction, which disinhibits subcortical dopamine structures and neurons.

Neuronal cultures from the knockout mice have demonstrated that synapsin I and II also have distinct roles in neuronal development.[21] Deletion of synapsin I retarded synapse formation, whereas deletion of synapsin II retarded axon formation. Deletion of both synapsins led to partial restoration of the wild phenotype; however, the development of the neurons was delayed.[22] This delay parallels the delay in reaching the adult phenotype observed in patients with schizophrenia. This animal model of synapsin-knockout mice is, like schizophrenia, development dependent and has elements of functional and trophic expression.

The atypical antipsychotic clozapine and the typical antipsychotic haloperidol have different effects in some animal models of schizophrenia.[23] Rats were treated with saline or pretreated with either clozapine or haloperidol followed by an injection of ketamine, the NMDA receptor antagonist. Saline alone had no effect on the prelimbic cortical area; however, ketamine produced an increase in the uptake of 2-deoxyglucose in the prelimbic cortical area, indicating an increase in neuronal metabolism. Pretreatment with haloperidol enhanced the induction of 2-deoxyglucose, whereas pretreatment with clozapine blocked the induction of 2-deoxyglucose so that the animal appeared identical to that treated with saline alone. Similar effects occurred in the hippocampus: ketamine increased 2-deoxyglucose uptake in the dentate gyrus, which was accentuated by haloperidol but blocked by clozapine.

These results parallel the effects of clozapine and haloperidol on ketamine-induced psychotic symptoms in schizophrenic patients. Clozapine blunts ketamine-induced increases in positive symptoms in patients with schizophrenia,[24] whereas haloperidol does not.[25]

CONCLUSIONS

These preliminary and diverse lines of investigation suggest that schizophrenia has more than one pathophysiologic process and that there may exist more than one mechanism of developing treatment resistance. One may be neurodevelopmental, such that patients have a severe form of the illness and are nonresponsive to treatment from the onset, whereas other patients may become treatment resistant during successive episodes. The therapeutic strategies for preventing these 2 forms of treatment resistance may need to be different. Although it is unclear whether atypical antipsychotics can restore the neurodevelopmental deficits, research on the animal model suggests that clozapine, and possibly other atypical drugs, may prevent the pathophysiologic process responsible for the neuroprogressive form of the illness.

Drug names: clozapine (Clozaril, Leponex), haloperidol (Haldol and others).

REFERENCES

1. Fish B. Neurobiologic antecedents of schizophrenia in children: evidence for an inherited, congenital neurointegrative defect. Arch Gen Psychiatry 1977;34:1297–1313
2. Lieberman J, Jody D, Geisler S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry 1993;50:369–376
3. Thome J, Foley P, Riederer P. Neurotrophic factors and the maldevelopmental hypothesis of schizophrenic psychoses. J Neural Transm 1998;105: 85–100
4. Marx CE, Vance BJ, Jarskog LF, et al. Neurotrophic factor levels in human amniotic fluid. In: New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association; June 1, 1998; Toronto, Ontario, Canada. Abstract NR113:98
5. Degreef G, Ashtari M, Bogerts B, et al. Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. Arch Gen Psychiatry 1992;49:531–537
6. Owen MJ, Lewis SW, Murray RM. Obstetric complications and schizophrenia: a computed tomographic study. Psychol Med 1988;18:331–339
7. Alvir JMJ, Woerner MG, Gunduz H, et al. Obstetric complications predict treatment response in first episode schizophrenia. Psychol Med. In press
8. McGlashan TH. A selective review of recent North American long-term follow-up studies of schizophrenia. Schizophr Bull 1988;14:515–542
9. Lieberman JA, Alvir JM, Koreen A, et al. Psychobiologic correlates of treatment response in schizophrenia. Neuropsychopharmacol 1996;14 (3, suppl):13S–21S
10. Loebel AD, Lieberman JA, Alvir JM, et al. Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry 1992;149:1183–1188
11. Lieberman JA, Alvir JM, Woerner M, et al. Prospective study of psychobiology in first episode schizophrenia at Hillside Hospital: design, methodology, and summary of findings. Schizophr Bull 1992;18:351–371
12. DeLisi TE, Twe W, Shu-hong X, et al. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. Biol Psychiatry 1995;38:349–360
13. Gur RE, Cowell P, Turetsky BI, et al. A follow-up magnetic resonance imaging study of schizophrenia. Arch Gen Psychiatry 1998;55:145–152
14. Rapoport JL, Giedd J, Kumra S, et al. Childhood-onset schizophrenia: progressive ventricular change during adolescence. Arch Gen Psychiatry 1997;54:897–903
15. Lieberman JA, Sheitman B, Kinon BJ. Neurochemical sensitization in the pathophysiology of schizophrenia: deficits and dysfunction in neuronal regulation and plasticity. Neuropsychopharmacol 1997;17:205–229
16. Javitt DC, Frusciante MJ, Zukin SR. Activation-related and activation-independent effects of polyamines on phencyclidine receptor binding within the *N*-methyl-D-aspartate receptor complex. J Pharmacol Exp Ther 1994;270:604–613
17. Tcherepanov AA, Sokolov BP. Age-related abnormalities in expression of mRNAs encoding synapsin 1A, synapsin 1B, and synaptophysin in the temporal cortex of schizophrenics. J Neurosci Res 1997;49:639–644
18. Grebb JA, Greengard P. An analysis of synapsin II, a neuronal phosphoprotein, in postmortem brain tissue from alcoholic and neuropsychiatrically ill adults and medically ill children and young adults. Arch Gen Psychiatry 1990;47:1149–1156
19. Kao HT, Porton B, Czernik AJ, et al. A third member of the synapsin gene family. Proc Natl Acad Sci U S A 1998;95:4667–4672
20. Rosahl TW, Spillane D, Missler M, et al. Essential functions of synapsins I and II in synaptic vesicle regulation. Nature 1995;375:488–493
21. Ferreira A, Chin LS, Li L, et al. Distinct roles of synapsin I and synapsin II during neuronal development. Mol Med 1998;4:22–28
22. Chin LS, Li L, Ferreira A, et al. Impairment of axonal development and of synaptogenesis in hippocampal neurons of synapsin I-deficient mice. Proc Natl Acad Sci U S A 1995;92:9230–9234
23. Duncan GE, Leipzig JN, Mailman RB, et al. Differential effects of clozapine and haloperidol on ketamine-induced brain metabolic activation. Brain Res 1998;812:65–75
24. Malhotra AK, Adler CM, Kennison SD, et al. Clozapine blunts N-methyl-D-aspartate antagonist-induced psychosis: a study with ketamine. Biol Psychiatry 1997;42:664–668
25. Lahti AC, Koffel B, LaPorte D, et al. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacol 1995;13: 9–19