Readdressing synaptic pruning theory for schizophrenia
Combination of brain imaging and cell biology

Akiko Hayashi-Takagi,1 Peter B. Barker2 and Akira Sawa1,3,*
1Departments of Psychiatry, 2Radiology and 3Neuroscience; Johns Hopkins University School of Medicine; Baltimore, MD USA

Disturbance in the synapse has been suggested in the pathology of schizophrenia, especially through examination of autopsied brains from patients with the disease. Nonetheless, it has been unclear whether and how such disturbance is associated with the onset and progression of the disease in young adulthood. Some studies with magnetic resonance spectroscopy (MRS) have suggested that overpruning of dendritic spines may occur in the prodromal and early stages of schizophrenia. In addition, our recent study indicates that DISC1, a promising risk factor for schizophrenia, has a crucial role in the maintenance of the dendritic spine in association with activation of the NMDA-type glutamate receptor.1 Disturbance of spine maintenance can be linked to aberrant synaptic pruning during postnatal brain maturation. Biological studies with genetic models may provide us with an opportunity to validate experimentally the synaptic pruning theory for schizophrenia. An integrative strategy of brain imaging and cell biology may be a promising approach to address a key biological question for mental illnesses.

Schizophrenia is a debilitating and common mental disorder, and its mechanistic understanding at the molecular and cellular levels is awaited. Involvement of genetic factors in the etiopathogenesis of schizophrenia is clear, but no specific causal gene, such as huntingtin for Huntington’s disease, has been reported for this mental disorder. Instead, a combination of genetic and environmental factors may contribute synergistically to the pathology from early development to the onset after puberty.2 The pathology appears to include dysfunction of glutamatergic neurotransmission in the cerebral cortex of schizophrenia patients.3 Several studies with autopsied brains from patients with schizophrenia have reported a reduced density of the dendritic spine,4 the main microstructure of the glutamate synapses,5 but how such spine defects become prominent in brains of patients with schizophrenia remains unclear.

Over the last decade and a half, schizophrenia has been extensively studied by in vivo magnetic resonance spectroscopy (MRS) by using conventional localized spectroscopy methods.6-8 Although findings have sometimes been discordant, several reasonably consistent patterns have emerged. For instance, 31P MRS studies have found decreased phospho monoesters (PME) and increased phosphodiesters (PDE) in the frontal lobes of patients with schizophrenia relative to normal control subjects.9 It appears that the increased PDE levels are found only in the early phases of schizophrenia, not in chronic cases.10,11 This suggests that schizophrenia patients have abnormal phospholipid metabolism in their frontal lobe membranes, with decreased synthesis and increased breakdown of neuronal membrane phospholipids. This finding is likely to be consistent with a proposal that the synaptic defects found in autopsied brains from patients with schizophrenia might come from overpruning of the synapse,12 that is, excess loss of the neuronal membrane.13

What possible mechanisms could underlie such synaptic changes in
association with schizophrenia? Genetic susceptibility factors for schizophrenia may provide us with important clues. For the past several years, efforts to elucidate functions of genetic factors in schizophrenia have been made in many laboratories, including ours. As described above, none of the genes cause this disease per se; nonetheless many of the susceptibility factors are enriched in the synapse.\textsuperscript{14} Therefore, we hypothesized that these factors may be functionally related with one another, forming biologically significant “pathways” and playing a role in synaptic maintenance.\textsuperscript{3} Thus, genetic variations or mutations in these factors may lead to overpruning of the synapse in young adolescents. Disrupted-in-Schizophrenia 1 (DISC1) may be a leading candidate for understanding synaptic change in schizophrenia.

We have found that the protein binding of DISC1 and Kalirin-7 (Kal-7) is regulated by activation of the NMDA-type glutamate receptor.\textsuperscript{1} Kal-7 is known to regulate structural plasticity of the dendritic spine via controlling Rac1 activity.\textsuperscript{15} Expression of Kal-7 is reportedly decreased in brains from patients with schizophrenia.\textsuperscript{16} DISC1 inhibits Kal-7 from accessing Rac1; whereas, once the NMDA receptor is activated, DISC1 dissociates from Kal-7 and enables it to activate Rac1. Rac1 activity is required for spine growth, but excess activity is against spine maintenance.\textsuperscript{17,18} Thus, our experimental data indicate that DISC1 is required for proper spine maintenance. Although many genetic studies have suggested that DISC1 is a promising risk factor for schizophrenia, it is unclear how DISC1 is involved in the pathology. In the synapse, loss of DISC1 elicits increased access of Kal-7 to Rac1, resulting overactivation of Rac1 and shrinkage of the synaptic spine, demonstrated in experiments with RNAi to DISC1 in vitro and in vivo. Overexpression of DISC1 (gain of function) also augments inhibition of Kal-7, leading to insufficient activation of Rac1 and spine shrinkage in prolonged neuron culture. Taken together, various alterations in DISC1, both loss and gain of functions, apparently result in a common synaptic disturbance. Longitudinal study of synaptic morphology and function with genetic animal models of schizophrenia, such as DISC1 mutant models, from early development to adulthood may provide an opportunity to validate this synaptic pruning theory for schizophrenia experimentally.

In summary, we introduce the synaptic pruning theory for schizophrenia and summarize efforts to validate this notion experimentally. Combination of brain imaging, especially MRS, with patients with schizophrenia together with longitudinal studies of genetic animal models for the disease may be an attractive approach to address this question.

Acknowledgements

This work was supported by USPHS grants of MH-084018 Silvio O. Conte center (A.S.), MH-069853 (A.S.), MH-085226 (A.S.), MH-088753 (A.S.), as well as grants from Stanley (A.S.), RUSK (A.S.), S-R (A.S.), Maryland Stem Cell Research Fund (A.S.) and NARSAD (A.H.T. and A.S.).

References

1. Hayashi-Takagi A, Takaki M, Graziante N, Seshadi S, Mur doch H, Dunlop AJ, et al. Disrupted-in-Schizophrenia 1 (DISC1) regulates spines of the glutamate synapse via Rac1. Nat Neurosci 2010; 13:327-32.
2. Hayashi-Takagi A, Sawa A. Disturbed synaptic connectivity in schizophrenia: Convergence of genetic risk factors during neurodevelopment. Brain Res Bull 2010; 83:140-6.
3. Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 2001; 158:1367-77.
4. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry 2000; 57:65-73.
5. Kasai H, Fukuda M, Watanabe S, Hayashi-Takagi A, Noguchi J. Structural dynamics of dendritic spines in memory and cognition. Trends Neurosci 2010; 33:121-9.
6. Lysy IK, Renshaw PF. Magnetic resonance spectroscopy: current and future applications in psychiatric research. Biol Psychiatry 2002; 51:95-207.
7. Berolina A, Nawroz S, Martay VS, Barnett AS, Duy n JH, Moonten CT, et al. Regionally specific pattern of neurochemical pathology in schizophrenia as assessed by multislice proton magnetic resonance spectroscopic imaging. Am J Psychiatry 1996; 153:1554-62.
8. Steen BG, Hamer RM, Lieberman JA. Measurement of brain metabolites by ¹H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. Neuropsychopharmacology 2005; 30:1949-62.
9. Keshavan MS, Stanley JA, Petregrew JW. Magnetic resonance spectroscopy in schizophrenia: Methodological issues and findings—part II. Biol Psychiatry 2000; 48:389-60.
10. Stanley JA, Williamson PC, Drost DJ, Carr TJ, Rylett RJ, Morrison-Stewart S, et al. Membrane phospholipid metabolism and schizophrenia: an in vivo ³¹P-MR spectroscopy study. Schizophr Res 1994; 13:209-15.
11. Stanley JA, Williamson PC, Drost DJ, Carr TJ, Rylett RJ, Malla A, et al. An in vivo study of the prefrontal cortex of schizophrenic patients at different stages of illness via phosphorus magnetic resonance spectroscopy. Arch Gen Psychiatry 1995; 52:399-406.
12. Feinberg I. Schizophrenia: caused by a fault in programed synaptic elimination during adolescence? J Psychiatr Res 1982; 17:319-34.
13. Petregrew JW, Keshavan MS, Minshew NJ. ³¹P nuclear magnetic resonance spectroscopy: neurodevelopment and schizophrenia. Schizophr Bull 1993; 19:35-53.
14. Harrison PJ, West VA. Six degrees of separation: on the prior probability that schizophrenia susceptibility genes converge on synapses, glutamate and NMDA receptors. Mol Psychiatry 2006; 11:981-3.
15. Pennesi F, Jones KA. Dendritic spine dynamics—a key role for kalirin-7. Trends Neurosci 2008; 31:419-27.
16. Hill JJ, Hashimoto T, Lewis DA. Molecular mechanisms contributing to dendritic spine alterations in the prefrontal cortex of subjects with schizophrenia. Mol Psychiatry 2006; 11:557-66.
17. Luo L, Hensch TK, Ackerman L, Barbel S, Jan LY, Jan YN. Differential effects of the Rac GTPase on Purkinje cell axons and dendritic trunks and spines. Nature 1996; 379:837-40.
18. Tashiro A, Minden A, Yuste R. Regulation of dendritic spine morphology by the rho family of small GTPases: antagonistic roles of Rac and Rho. Cereb Cortex 2000; 10:927-38.