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Research report

Disturbed synaptic connectivity in schizophrenia: Convergence of genetic risk factors during neurodevelopment

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ABSTRACT

The pathological mechanisms underlying schizophrenia are unclear. Although genetic susceptibility factors for schizophrenia likely influence neurodevelopmental processes, the onset of the disease is in adolescence and young adulthood. Here we review recent literatures implicating neurodevelopmental deficits in schizophrenia and discuss how genetic factors are involved in the processes toward onset of the disease. We emphasize the importance of postnatal glutamate synapse development in the pathology of the disorder. These genetic risk factors contribute to the process possibly in a synergistic manner. The notion of signal pathways involving more than one genetic factor is in accord with the multifactorial nature of schizophrenia.

1. Introduction

Schizophrenia (SZ) is a chronic and devastating mental illness whose lifetime prevalence is estimated as 0.72% [84,94]. The onset of the disease is primarily in adolescence and adulthood, and the onset in males is several years earlier that of females [94]. Clinical and pharmacological studies have indicated that disturbances of dopaminergic [35,23,143,39,133], glutamatergic [52,99], and gamma-aminobutyric acid (GABA) transmission [85,9] participate in the pathophysiology of SZ in adulthood. In contrast, various lines of evidence have supported involvement of risks and insults during neurodevelopment in the etiopathogenesis of the disorder [142,22,112]. Several genetic risk factors for SZ have been identified in the past several years [105,61,4,129]. Thus far, no single factor that plays causal role for SZ, such as Huntingtin for Huntington's disease [2], has been reported. Instead, these risk factors seem to operate synergistically in similar biological contexts, especially during neurodevelopment and glutamate-associated signaling. Biological understanding of genetic risk factors may be able to link neurodevelopmental etiopathogenesis to adult onset and pathophysiology of SZ [61]. Thus, we will pay particular attention to genetic risk factors for SZ, especially those associated with development and plasticity of glutamate synapses. Here we will review processes involved in normal brain development and discuss how SZ patients may have deficits in these processes.

2. Neurodevelopment and SZ

2.1. Normal brain development

The development of central nervous system (CNS) is a precise cascade of numerous biological processes. In early brain development, corresponding to pre- and perinatal periods, progenitor cell proliferation and neural differentiation, migration of immature neurons to their final positions, and neurite outgrowth/arborization occur in a temporally and spatially precise manner [37,70,72]. Genetic factors are believed to be a key determinant, but many environmental factors, such as birth complications, can modulate the processes.

The brain continuously develops during postnatal periods. One of the most marked changes in postnatal brain development is reorganization of synapses, which include synaptic stabilization and elimination (pruning) [12,78]. During late adolescence, synaptic protein composition changes [51]. For example, the subunit composition of the *N*-methyl-D-aspartate-type glutamate receptor (NMDA-R) is changed from the NR2B into the NR2A isoform [139], which is followed by an increase in surface expression of α-amino-3-hydroxyl-5-methyl-4-isoxazole propionate-type glutamate receptor (AMPA-R), causing robust changes in synaptic

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transmission [139]. The synapse density is also markedly altered during postnatal development. In a postmortem study on the middle frontal gyrus, it was found that synaptic density increases after birth until 2–5 years of age and then decreases steeply in early adolescence [73]. The eliminated synapses in this process of "synaptic pruning" are mainly glutamatergic [14]. Although the numbers of these asymmetric glutamatergic synapses decrease to less than one-third of the maximal level, that of symmetric synapses, such as GABAergic synapses is almost constant during this time [14]. Robust postnatal maturation of dopaminergic neurons, especially their mesocortical projections from the ventral tegmental area takes place in the postnatal period [10]. Maturation of GABAergic neurons includes alteration in expression of key molecules, such as GABA Transporter 1 (GAT1) and GABA-α2 receptor subunit [85], as well as dramatic changes in the response to dopamine [138].

Brain imaging studies indicate drastic reorganization of the brain during adolescence. Longitudinal studies with magnetic resonance imaging indicated that the gray matter volume of the frontal lobe increased during pre-adolescence to a maximum at 12 years of age and then decreased during post-adolescence [48,49] in contrast to the white matter volume of that lobe, which increased linearly with age [108]. As detected in magnetic resonance spectroscopy, levels of the glutamate synapse marker *N*-acetyl-aspartate also changes in adolescence [75]. Studies with positron emission tomography showed that the glucose metabolic rate in gray matter increases until 10 years of age and then decreases in early adolescence [29]. The amplitude of slow waves of the electroencephalogram and the latency of event-related potentials fall during adolescence [44]. Thus, dynamic structural and functional reorganization of the brain continues until young adulthood, at the timing of the onset of SZ.

2.2. Signs of abnormal brain development in SZ

Premorbid abnormalities are often reported in many, but not all, SZ patients, which support the idea that neurodevelopmental deficits are involved in this disorder. These include minor impairments in movement, attention, executive function, and language, as well as excessive solitary play and social anxiety before the onset of SZ [74,25,20].

Many studies have indicated involvement of risks and insults during early development, such as pre- and perinatal stages, in SZ. Urban birth and urbanicity during upbringing has been reported more frequently among individuals with SZ than in the general population [100,109]. Why this occurs is unclear, but exposure to deleterious factors, including infection, toxins, or malnutrition associated with urban environment have been suggested as possible mechanisms. Many studies have also found season of birth in the Northern hemisphere to be a risk factor for SZ with 5–8% more individuals with SZ born in the winter and spring than in the summer and fall, which some have interpreted as evidence of risk posed by elevated winter infections [100,134]. Traces of congenital infection with the protozoan Toxoplasma gondii and diverse viruses (cytomegalovirus, rubella, herpes simplex virus, and influenza) have been found in SZ cases [95,40,15,18,24,148,145]. Obstetrical complications, especially birth hypoxia, are reportedly a major risk factor for SZ, and the odds ratio of the labor-delivery complications on the development of SZ is 2.0 [21]. Consistent with these observations, SZ patients frequently have minor physical anomalies [54,55,93,67,31,136], such as strabismus, small head, high-arched palate, and low-set ears, which are the result of brain damage during the first and second trimesters.

Although many lines of evidence have suggested involvement of brain insults in early (pre- and perinatal) development for the pathology of SZ, the onset of the disorder is most common in adolescence and young adulthood. This suggests that such deficits in early development may, in most cases, could increase the risk for the disease, but are insufficient for the onset. Nonetheless, factors that determine the SZ onset in young adulthood remain elusive. Although no study has directly addressed this issue experimentally, dysregulated changes of synaptic spines in adolescence, excess synaptic pruning [44,79], might account for this question. If this is the case, decrease in gray matter volume [132,107,140], glucose metabolic rate [5], and the level of *N*-acetyl-aspartate [11,124] in many cases of SZ might be well explained.

Thus far, there have been two major proposals to address this question: the first one proposed by Feinberg suggests that *the defect in a profound reorganization of human brain function may underlie those cases of schizophrenia that emerge during adolescence* [44]. The second one proposed by Weinberger suggests *a fixed "lesion" from early in life interacts with normal brain neurodevelopmental events that occur much later* [142]. It is reasonable that SZ risk factors are involved in both ways: "pre-existing SZ lesion" and altered "profound reorganization during adolescence."

2.3. Suggestive evidence implicating synaptic disturbances in SZ patients

Neuropathological examination of autopsied brains from patients is in accord with the idea that abnormal synaptic reorganization, such as synaptic pruning, may occur in SZ [119]. Unlike brains from patients with neurodegerative disorders, SZ brains do not show massive neuronal cell loss and glial cell proliferation, but display subtle abnormalities in cytoarchitecture, especially reduced neuropil volume [119,63]. The neuropil is an interneuronal space that consists of neural process and synapse, including dendritic spines. Three independent groups used a Golgi impregnation method and consistently reported that density of the glutamate dendritic spines on pyramidal neurons was decreased in the forebrain from SZ patients [50,47,81,117]. This is consistent with a neuroimaging study, which suggests that there is altered glutamate receptor binding in the prefrontal cortex, thalamus, and hippocampus in SZ patients [111], and is supported by molecular biological studies suggesting that glutamatergic spines may be altered in SZ as reflected in decreased levels of molecules that regulate spine structure, such as Rho GTPase family molecules (*e.g.*, Cdc42, Rac1, and RhoA) and Rac1 activator Kalirin-7 in the dorsolateral PFC from 15 matched pairs of SZ and controls [71]. Microarray studies, an unbiased approach for gene expression profiling, show a decrease in the group of transcripts encoding for proteins that regulate synaptic functions [98]. In studies with autopsied brains, the results might be affected by long-term medication in the subjects and other confounding factors [86,64,59]. Nonetheless, it is reported that antipsychotics do not reduce the dendritic spine density [32], number of neurons [82], nor expression of neural markers [103], suggesting that synaptic changes in SZ brains are due to the illness but not the effect of antipsychotics. Consistent with this view, computer simulation supports synaptogenesis and subsequent synaptic pruning could account for the typical age of onset, course, and symptoms of SZ [92]. If disturbance of synaptic connectivity is a key alteration in SZ, what causes this disruption? We may begin to answer this question by considering the neurobiology of recently identified genetic risk factors for SZ [61].

3. Genetic risk factors for SZ: synergistic roles for glutamate synapse development

3.1.1. Genetic studies of SZ

Family, twin, and adoption studies of SZ patients have indicated the involvement of genetic factors in the etiopathogenesis