Schizophrenia Bulletin vol. 40 no. 5 pp. 952–957, 2014
doi:10.1093/schbul/sbu111
Advance Access publication July 22, 2014

Early Developmental Disturbances of Cortical Inhibitory Neurons: Contribution to Cognitive Deficits in Schizophrenia

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Cognitive dysfunction is a disabling and core feature of schizophrenia. Cognitive impairments have been linked to disturbances in inhibitory (gamma-aminobutyric acid [GABA]) neurons in the prefrontal cortex. Cognitive deficits are present well before the onset of psychotic symptoms and have been detected in early childhood with developmental delays reported during the first year of life. These data suggest that the pathogenetic process that produces dysfunction of prefrontal GABA neurons in schizophrenia may be related to altered prenatal development. Interestingly, adult postmortem schizophrenia brain tissue studies have provided evidence consistent with a disease process that affects different stages of prenatal development of specific subpopulations of prefrontal GABA neurons. Prenatal ontogeny (ie, birth, proliferation, migration, and phenotypic specification) of distinct subpopulations of cortical GABA neurons is differentially regulated by a host of transcription factors, chemokine receptors, and other molecular markers. In this review article, we propose a strategy to investigate how alterations in the expression of these developmental regulators of subpopulations of cortical GABA neurons may contribute to the pathogenesis of cortical GABA neuron dysfunction and consequently cognitive impairments in schizophrenia.

Key words: parvalbumin/somatostatin/prefrontal cortex/interneuron/GABA neuron/prenatal ontogeny/postmortem/development

Introduction

Schizophrenia is frequently associated with a lifetime of impairment in social and occupational domains and premature mortality.[1,2] While the diagnostic clinical features of schizophrenia include positive or psychotic symptoms and negative symptoms, poor long-term outcomes in individuals with schizophrenia have been principally linked to the severity of cognitive dysfunction in the illness.[3] Cognitive impairments in schizophrenia include deficits in selective attention, declarative memory, working memory, and cognitive control.[4] Cognitive dysfunction represents a core impairment in schizophrenia because cognitive deficits are common and relatively stable across the course of the illness, are present regardless of psychotic symptoms, and are found to a lesser degree in unaffected relatives.[5,6] Furthermore, the lack of responsiveness of cognitive deficits to available antipsychotic medications[7,8] indicates the need for greater insight into the pathogenetic processes that lead to the appearance of cognitive dysfunction in the illness.

Interestingly, cognitive disturbances are present prior to the onset of psychotic symptoms that typically occurs in late adolescence and early adulthood,[9] which suggests that the disease process that underlies cognitive problems may disrupt the normal maturation of cortical circuits (previously reviewed).[10,11] However, developmental delays have also been observed in early childhood,[12] even prior to the first birthday,[13–15] in individuals who go on to develop schizophrenia. These and other findings have led to the hypothesis that the disease process that ultimately leads to the appearance of clinical symptoms of schizophrenia in late teens/early 20s could actually have its origins in utero.[16,17] Consistent with this hypothesis, environmental insults that occur while in utero, such as maternal exposure to infection, have been linked to higher rates of schizophrenia.[18] However, further investigation of the role of prenatal insults in the pathogenesis of schizophrenia requires a consideration of the components of cortical pathology that may subserve cognitive impairments and how disturbances in the prenatal ontogeny of this cortical circuitry may contribute to the nature of cortical circuitry dysfunction in the illness.

Disturbances in Prefrontal GABA Neurons Contribute to Cognitive Dysfunction in Schizophrenia

Cognitive processes such as working memory are supported by the synchronized firing of groups of cortical pyramidal neurons at gamma frequencies (30–80 Hz).[19] Individuals with schizophrenia show altered gamma oscillation activity in the prefrontal cortex while performing cognitive tasks.[20,21] Gamma oscillations are subserved by a subpopulation of cortical inhibitory (gamma-aminobutyric acid [GABA]) neurons that contain the calcium-binding protein parvalbumin and provide powerful perisomatic inhibitory control over pyramidal neuron output. Disturbing the function of parvalbumin neurons leads to lower gamma oscillatory power.[22,23] Consequently, the presence of a disease-related disturbance in parvalbumin neurons would be predicted to interfere with the regulation of pyramidal neuron activity and gamma oscillations and lead to deleterious effects on cognition in schizophrenia.[24]

Interestingly, some of the most consistently reported postmortem brain tissue findings in schizophrenia involve disturbances in parvalbumin neurons in the prefrontal cortex. For example, lower parvalbumin mRNA levels have been reported in prefrontal cortex gray matter homogenates in multiple different cohorts of schizophrenia subjects[25–28] and do not appear to be attributable to antipsychotic medications.[25,28] Furthermore, approximately half of parvalbumin neurons in the prefrontal cortex in schizophrenia fail to express detectable mRNA levels for the GABA synthesizing enzyme GAD67,[25] and protein levels of parvalbumin and GAD67 have been reported to be reduced in parvalbumin axon terminals in the illness.[29,30] In addition, voltage-gated potassium channels are involved in the fast repolarization of neurons that allow high frequency firing such as gamma oscillations.[31] Interestingly, transcript levels of several voltage-gated potassium channels that are selectively found in parvalbumin neurons, including Kv3.1 and KCNS3, which encode the Kv9.3 modulatory α subunit,[31,32] are lower in the prefrontal cortex in schizophrenia.[33,34] Taken together, these disturbances in biochemical markers important for the gamma oscillation-related function of parvalbumin neurons may provide a substrate for some of the cognitive disturbances observed in schizophrenia.

Alteration in Subpopulations of Cortical GABA Neurons Are Consistent With a Prenatal Origin in Schizophrenia

Recent studies have provided insight into the prenatal ontogeny (ie, neuronal birth, proliferation, migration, and phenotypic specification) of different subpopulations of cortical GABA neurons. In humans, (future) parvalbumin neurons, and another subpopulation of cortical GABA neurons that express the neuropeptide somatostatin, begin to be born and proliferate by the 8th week of gestation in the medial ganglionic eminence of primordial basal ganglia, then begin to migrate tangentially to the cerebral cortex.[35–41] In contrast to parvalbumin and somatostatin neurons, the subpopulation of cortical GABA neurons that express the calcium-binding protein calretinin appears to largely originate from the caudal ganglionic eminence and possibly also from the subventricular zone of the dorsal pallium.[38–44] Phenotypic specification involves the ongoing process of developing cell-type-specific expression patterns of biochemical markers, electrophysiological properties, and anatomical features that differentiate neurons into subclasses such as parvalbumin, somatostatin, and calretinin neurons. Furthermore, as discussed in the next section, many transcription factors and other molecular markers are required for various stages of prenatal ontogeny of cortical GABA neurons.

Interestingly, the pattern of evidence from postmortem human brain tissue studies suggests that disturbances in parvalbumin neurons may originate during prenatal ontogeny. First, lower mRNA levels for somatostatin, but not calretinin,[25,28] have also been consistently observed in the prefrontal cortex across multiple cohorts of schizophrenia subjects.[26–28,45] Furthermore, parvalbumin and somatostatin mRNAs have been reported to be primarily lower in the same schizophrenia subjects identified as having a "low-GABA-marker" molecular phenotype (approximately half of all schizophrenia subjects studied), while the other schizophrenia subjects show no abnormalities in either parvalbumin or somatostatin mRNA in the prefrontal cortex.[28] Thus, a selective disturbance in cortical parvalbumin and somatostatin neurons, but not calretinin neurons, in the same schizophrenia subjects may potentially be explained by a pathogenetic process early in development that selectively affects neurons originating from the medial ganglionic eminence.

Second, the characteristics of disturbances in parvalbumin and somatostatin neurons suggest that different stages of prenatal ontogeny may be disrupted in schizophrenia. For example, a full complement of parvalbumin neurons appears to present in the prefrontal cortex in schizophrenia.[25,46] However, approximately half of parvalbumin neurons lack detectable mRNA levels of GAD67,[25] which suggests that parvalbumin neurons may migrate normally but fail to fully complete phenotypic specification.[47] Similarly, in situ hybridization studies of the prefrontal cortex in schizophrenia have also found that detectable somatostatin neurons express lower somatostatin mRNA levels.[45,48] However, in contrast to the findings with parvalbumin neurons in schizophrenia, fewer somatostatin neurons were detectable in the gray matter, while more somatostatin neurons were detectable in the white matter of the prefrontal cortex in the illness.[45,48] Thus, available data from postmortem human brain tissue studies are at least consistent with a disease

process that interferes with the migration of some somatostatin neurons in cortical white matter early in development and leads to an incomplete phenotypic specification of the cortical parvalbumin and somatostatin neurons that complete the migration process. Consistent with this hypothesis, other studies have also observed a higher density of interstitial white matter neurons in the prefrontal cortex in schizophrenia.[49–52] This evidence from postmortem human brain tissue studies, in combination with clinical findings of developmental delays in the first year of life,[13–15] raises the hypothesis that selective disturbance in subpopulations of cortical GABA neurons may begin during the period of prenatal ontogeny in schizophrenia. Understanding potential pathogenetic mechanisms that could selectively disrupt the development of parvalbumin and somatostatin neurons next requires a consideration of the factors that regulate prenatal GABA neuron ontogeny and how disturbances in the expression levels of these ontogenetic factors in schizophrenia may contribute to cortical GABA neuron dysfunction in the illness.

Transcription Factors, Chemokine Receptors, and Other Molecular Markers Regulate the Prenatal Development of Cortical Parvalbumin and Somatostatin Neurons

Numerous transcription factors, which are proteins that selectively bind to specific regions of DNA and regulate the transcription of mRNAs, are required for the normal migration, phenotypic specification, maturation, and survival of specific subpopulations of cortical GABA neurons. For example, multiple cell-type-specific transcription factors such as Nkx2.1, Sox6, MafB, Zeb2 (also known as Sip1 and Zfhx1b), Dlx5, and Dlx6 are expressed early in gestation in the medial ganglionic eminence and regulate the migration, specification, and maturation of cortical parvalbumin and somatostatin, but not calretinin, neurons.[37,53–60] Some molecular markers appear to be particularly important for the development of cortical parvalbumin neurons. For example, certain developmental regulators including the chemokine receptors CXCR4 and CXCR7 and the scaffold protein Disrupted-in-Schizophrenia 1 (DISC1) are all strongly expressed in the medial ganglionic eminence and are necessary for the migration of cortical parvalbumin neurons to the cerebral cortex.[61–65] In addition, the receptor tyrosine kinase for the trophic factor neuregulin 1, ErbB4, regulates the migration of cortical parvalbumin neurons and the development of excitatory synapses onto parvalbumin neurons.[66–68] In contrast, the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator 1α begins to be expressed postnatally by parvalbumin neurons and is essential for complete development of the parvalbumin neuron phenotype.[69]

While there is considerable overlap with the molecular markers that regulate parvalbumin neuron development, some developmental regulators appear to be more specific for somatostatin neuron development. For example, ontogenetic transcription factor Dlx[70] does not appear to be required for the tangential migration of cortical GABA neurons, but is required for postnatal expression of GAD67.[71] Postnatally, Dlx1 continues to be expressed by somatostatin neurons, but not parvalbumin neurons, and a complete loss of Dlx1 leads to a failure of cortical somatostatin, but not parvalbumin neurons, to survive into adulthood.[71] In addition, after neuronal migration is complete, most cortical parvalbumin and somatostatin, but not calretinin, neurons begin to express the nuclear matrix and genome organizer Special AT-rich DNA Binding Protein 1 (SATB1).[72] A complete loss of SATB1 does not appear to affect parvalbumin neurons but instead leads to substantially lower somatostatin mRNA and protein levels without affecting cell number, which indicates a role in the terminal differentiation and maturation of somatostatin neurons.[72]

Altered Expression of Transcription Factors and Other Developmental Regulators Might Contribute to Cortical Parvalbumin and Somatostatin Neuron Dysfunction in Schizophrenia

Taken together, the critical and varied roles of these (and many more) ontogenetic transcriptional regulators and chemokine receptors in the different stages of development of cortical parvalbumin and somatostatin neurons suggest that a disturbance in their expression or function could plausibly produce the pattern of deficits in parvalbumin and somatostatin neurons observed in the prefrontal cortex in schizophrenia. Interestingly, recent studies have reported abnormalities in these developmental regulators in schizophrenia. For example, lower Dlx1 mRNA levels have been reported in the orbital frontal cortex in subjects with schizophrenia.[73] Given the important role that Dlx1 has been reported to play in the postnatal development and survival of cortical somatostatin neurons,[71] deficits in Dlx1 may potentially contribute to some of the disturbances reported in somatostatin neurons, including lower somatostatin mRNA levels and fewer detectable somatostatin neurons, in schizophrenia.[45] In contrast, higher mRNA levels for a splice variant of ErbB4, termed JMa, have been reported in the prefrontal cortex in multiple cohorts of schizophrenia subjects.[74–76] Because the ErbB4-JMa splice variant is extracellular and is susceptible to proteolytic cleavage,[77] Weickert and colleagues have hypothesized that higher ErbB4-JMa levels may interfere with neuregulin signaling in schizophrenia,[76] which may in turn disrupt the migration of, and development of excitatory inputs to, cortical parvalbumin neurons in the disorder.[66–68] Furthermore, DISC1, which is important for the tangential migration of future cortical parvalbumin neurons,[64,65] was previously identified as a susceptibility gene for schizophrenia.[78] In addition,

recent genome-wide association studies have implicated Zeb2, another ontogenetic transcription factor involved in cortical parvalbumin and somatostatin neuron development,[59,60] as a candidate gene that provides increased risk for schizophrenia.[79]

However, the prenatal ontogeny of cortical parvalbumin and somatostatin neurons cannot be directly studied in schizophrenia and instead requires a multifaceted approach to investigate the role of prenatal disturbances in the development of cortical GABA neuron dysfunction in schizophrenia. First, the use of postmortem human brain tissue studies allows the identification of developmental factors that are consistently altered in expression in schizophrenia and the determination of whether the pattern of deficits in developmental factors is consistent with the observed alterations in cortical parvalbumin and somatostatin neurons in schizophrenia. Second, the use of postmortem brain tissue studies from a wide range of postnatal ages of monkeys, which have a more similar composition of cortical GABA neuron subpopulations and extended period of postnatal development to humans, allows a determination of whether altered expression of transcription factors in schizophrenia is more similar to an altered postnatal developmental trajectory, as has been reported for other parvalbumin neuron markers.[10,11,80] Finally, animal models that mirror the magnitude and cell-type specificity of the deficits in ontogenetic factors observed in schizophrenia are needed to provide construct validity for models of disrupted prenatal ontogeny of cortical parvalbumin and somatostatin neurons in schizophrenia.

In this issue, we utilize this cross-species approach to investigate another important transcription factor, Lhx6, that is selectively expressed by, and involved in the prenatal developmental of, cortical parvalbumin and somatostatin neurons.[32,81–83] Investigating the expression level of Lhx6 in the prefrontal cortex in schizophrenia subjects, the pattern of postnatal development of Lhx6 in the prefrontal cortex of monkeys, and the effects of a partial, cell-type specific loss of Lhx6 that mimics Lhx6 deficits in schizophrenia helps provide a framework for the process of investigating potential disruptions in prenatal development in schizophrenia. This approach may serve as a useful strategy for defining the pathogenesis of cortical circuit dysfunction in schizophrenia and for identifying the molecular mechanisms that are vulnerable to environmental events at different stages of development. This knowledge may inform both the type and timing of preemptive interventions for cognitive dysfunction in schizophrenia.

Funding

The National Institutes of Health (MH100066 to D.W.V., MH043784 and MH051234 to D.A.L.).

Acknowledgment

Disclosure: David A. Lewis currently receives investigator-initiated research support from Bristol-Myers Squibb and Pfizer and in 2012–2014 served as a consultant in the areas of target identification and validation and new compound development to Autifony, Bristol-Myers Squibb, Concert Pharmaceuticals, and Sunovion. Dr Volk has nothing to disclose.

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