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PRENATAL ONTOGENY AS A SUSCEPTIBILITY PERIOD FOR CORTICAL GABA NEURON DISTURBANCES IN SCHIZOPHRENIA

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Abstract—Cognitive deficits in schizophrenia have been linked to disturbances in GABA neurons in the prefrontal cortex (PFC). Furthermore, cognitive deficits in schizophrenia appear well before the onset of psychosis and have been reported to be present during early childhood and even during the first year of life. Taken together, these data raise the following question: Does the disease process that produces abnormalities in prefrontal GABA neurons in schizophrenia begin prenatally and disrupt the ontogeny of cortical GABA neurons? Here, we address this question through a consideration of evidence that genetic and/or environmental insults that occur during gestation initiate a pathogenetic process that alters cortical GABA neuron ontogeny and produces the pattern of GABA neuron abnormalities, and consequently cognitive difficulties, seen in schizophrenia. First, we review available evidence from postmortem human brain tissue studies characterizing alterations in certain subpopulations of prefrontal GABA neuron that provide clues to a prenatal origin in schizophrenia. Second, we review recent discoveries of transcription factors, cytokine receptors, and other developmental regulators that govern the birth, migration, specification, maturation, and survival of different subpopulations of prefrontal GABA neurons. Third, we discuss recent studies demonstrating altered expression of these ontogenetic factors in the PFC in schizophrenia. Fourth, we discuss the potential role of disturbances in the maternal–fetal environment such as maternal immune activation in the development of GABA neuron dysfunction. Finally, we propose critical questions that need to be answered in future research to further investigate the role of altered GABA neuron ontogeny in the pathogenesis of schizophrenia.

Key words: parvalbumin, somatostatin, prefrontal cortex, interneuron, development.

Contents

INTRODUCTION

Schizophrenia is a devastating psychiatric disorder that afflicts ~1% of all humans and is a leading cause of morbidity and early mortality (Insel and Scolnick, 2006). The features of the disorder with the strongest association to poor long-term outcomes include cognitive deficits (Green, 2006), such as impairments in working memory and cognitive control (Lesh et al., 2011). Disturbances in cognitive functioning are commonly seen in the illness (Keefe and Fenton, 2007) and certain cognitive deficits have been linked to the dysfunction of subsets of inhibitory (GABA) neurons in the prefrontal cortex (PFC) (reviewed in (Lewis et al., 2012) and discussed in greater detail below). Furthermore, cognitive dysfunction in schizophrenia is only minimally responsive to antipsychotic medications (Keefe et al., 2007a,b). This lack of effective treatments for the cognitive features of schizophrenia indicates the

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Abbreviation: PV, parvalbumin; PFC, prefrontal cortex; PGC-1α, proliferator-activated receptor γ coactivator 1α; SATB1, Special AT-rich DNA-Binding Protein 1; SST, somatostatin.

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need for greater insight into the pathogenetic processes that lead to disturbances in PFC GABA neurons.

Interestingly, cognitive disturbances are present before the onset of psychosis and well before the diagnosis of schizophrenia is typically made in late adolescence/early adulthood (Woodberry et al., 2008). These data suggest that the disease process affecting PFC GABA neurons is already active during development. In previous reviews, we discussed the potential role of postnatal developmental changes in PFC GABA neurons during adolescence in creating a sensitive period for environment insults, such as a cannabis exposure, that may lead to the emergence of PFC GABA neuron disturbances in schizophrenia (Beneyto and Lewis, 2011; Hoftman and Lewis, 2011). However, the initial onset of the disease process may begin at an even earlier stage of life. For example, individuals with schizophrenia exhibit delays in achieving developmental milestones in early childhood (Jones et al., 1994), even during the first year of life (Ridler et al., 2006; Sorensen et al., 2010; Clarke et al., 2011). Furthermore, *in utero* environmental insults, such as exposure to maternal infection, during the first and second trimester, which is the time period when cortical GABA neurons are born (Jakovcevski et al., 2011), are associated with an increased risk of schizophrenia in offspring (Brown and Derkits, 2010). In addition, murine models of maternal immune activation have been reported to disrupt the development of PFC GABA neurons (Meyer et al., 2008; Richetto et al., 2013).

Taken together, these data raise the following question: Could the disease process that produces the cortical GABA neuron disturbances present in adults with schizophrenia begin much earlier than adolescence, perhaps even prenatally? Here, we address this question through a consideration of the evidence supporting the idea that genetic and/or environmental insults during gestation could initiate a pathogenetic process that alters the development (e.g. migration, phenotypic specification, maturation, and survival) of cortical GABA neurons, resulting in the pattern of GABAergic alterations, and consequently cognitive difficulties, seen in the disorder. First, we review the wealth of data accumulated over the past decade characterizing alterations in subsets of PFC GABA neurons that are relevant for cognitive dysfunction and may provide clues to a prenatal pathogenetic origin in schizophrenia. Second, we review recent discoveries of developmental regulators that govern the birth, migration, specification, maturation, and survival of PFC GABA neurons. Third, we discuss recent studies demonstrating altered expression of these ontogenetic factors in the PFC in schizophrenia. Fourth, we discuss the potential role of disturbances in maternal–fetal environment in the development of GABA neuron dysfunction in schizophrenia. Finally, we propose critical questions that need to be answered in future research on the role of altered GABA neuron ontogeny in the pathogenesis of schizophrenia.

ALTERATIONS IN SUBPOPULATIONS OF PFC GABA NEURONS CONTRIBUTE TO COGNITIVE DYSFUNCTION AND PROVIDE CLUES TO A PRENATAL PATHOGENETIC ORIGIN IN SCHIZOPHRENIA

The most consistently reported disease-related findings in the PFC in schizophrenia involve GABA neurons. For example, deficits in mRNA levels for the GABA-synthesizing enzyme GAD67 have been replicated across multiple subject cohorts and do not appear to be attributable to antipsychotic medications (Akbarian et al., 1995; Guidotti et al., 2000; Volk et al., 2000; Vawter et al., 2002; Straub et al., 2007; Duncan et al., 2010; Curley et al., 2011). Interestingly, the majority of PFC GABA neurons appear to express normal levels of GAD67 mRNA in schizophrenia (Volk et al., 2000). Furthermore, approximately 50% of GABA neurons in primate PFC express the calcium-binding protein calretinin (Conde et al., 1994; Gabbott and Bacon, 1996). Calretinin mRNA levels have been reported to be unchanged in the PFC in schizophrenia (Hashimoto et al., 2003; Volk et al., 2012), suggesting that calretinin neurons are largely unaffected in the disorder.

However, two other subsets of GABA neurons have been consistently reported to be altered in the PFC of subjects with schizophrenia. For example, a subpopulation of GABA neurons identified as abnormal in schizophrenia includes those that express the calcium-binding protein parvalbumin (PV), which includes ~25% of PFC GABA neurons in primate PFC (Conde et al., 1994; Gabbott and Bacon, 1996). Lower PV mRNA levels in schizophrenia have also been consistently reported in PFC gray matter by different research groups (Hashimoto et al., 2003; Mellios et al., 2009; Fung et al., 2010; Volk et al., 2012). Diminished PV neuron regulation of pyramidal neuron activity may have negative consequences for cognitive functioning in schizophrenia (Lewis et al., 2012). Fast-spiking PV neurons provide powerful perisomatic inhibitory regulation of pyramidal neuron output and enable the synchronization of cortical neuron activity at gamma frequencies (30–80 Hz) (Sohal et al., 2009; Sohal, 2012). Gamma frequency oscillations are important for perceptual and PFC-related cognitive processes such as working memory (Howard et al., 2003), and individuals with schizophrenia show altered PFC gamma activity while performing tasks that require cognitive control (Cho et al., 2006; Minzenberg et al., 2010). Disrupting PV neuron function results in reduced gamma oscillatory power (Whittington et al., 1998; Gulyas et al., 2010). Thus, pathological processes affecting PV neurons may adversely affect the synchronization of cortical neural activity and contribute to cognitive dysfunction in schizophrenia.

Interestingly, *in situ* hybridization grain counting studies have found that PFC GABA neurons underexpress PV mRNA, but that the number of neurons expressing detectable PV mRNA levels in the PFC gray matter appears unchanged (Hashimoto et al., 2003). Similarly, immunohistochemistry studies have