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Behavioral and neurochemical consequences of cortical oxidative stress on parvalbumin-interneuron maturation in rodent models of schizophrenia

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ABSTRACT

Oxidative stress, in response to the activation of the superoxide-producing enzyme Nox2, has been implicated in the schizophrenia-like behavioral dysfunction that develops in animals that were subject to either neonatal NMDA receptor-antagonist treatment or social isolation. In both of these animal models of schizophrenia, an environmental insult occurring during the period of active maturation of the fast-spiking parvalbumin-positive (PV+) interneuronal circuit leads to a diminished expression of parvalbumin in GABA-inhibitory neurons when animals reach adulthood. The loss of PV+ interneurons in animal models had been tentatively attributed to the death of these neurons. However, present results show that for the perinatal NMDA-R antagonist model these interneurons are still alive when animals are 5–6 weeks of age even though they have lost their phenotype and no longer express parvalbumin. Alterations in parvalbumin expression and sensory-evoked gamma-oscillatory activity, regulated by PV+ interneurons, are consistently observed in schizophrenia. We propose that cortical networks consisting of faulty PV+ interneurons interacting with pyramidal neurons may be responsible for the aberrant oscillatory activity observed in schizophrenia. Thus, oxidative stress during the maturation window for PV+ interneurons by alteration of normal brain development, leads to the emergence of schizophrenia-like behavioral dysfunctions when subjects reach early adulthood.

This article is part of a Special Issue entitled 'Schizophrenia'.

1. Introduction

There is increasing evidence that schizophrenia, which typically presents in adolescence or early adulthood, is a consequence of errors in early brain development (Rapoport et al., 2005; Fatemi and Folsom, 2009). Several animal models are being used to understand neurobiological processes relevant to the developmental hypothesis of schizophrenia (Lipska and Weinberger, 2000; Fatemi and Folsom, 2009; Meyer and Feldon, 2009; Powell, 2010). These models have provided insight into the vulnerability of the developing embryo and the importance of the early environment for normal maturation. Developmental models specific to schizophrenia have focused on epidemiological risk factors (e.g., prenatal viral insult, birth complications) or more heuristic models aimed at understanding the developmental neuropathology of the disease (e.g., neonatal NMDA receptor (NMDA-R) antagonist administration, neonatal ventral hippocampal lesions). Combined approach of behavioral and neuroanatomical evaluation of these models strengthens their utility in improving our understanding of the pathophysiology of schizophrenia and developing new treatment strategies.

Data from genetic and neurodevelopmental animal models show that alterations of brain development during specific periods of pre or postnatal life produce a decrease in the expression of the calcium-binding protein parvalbumin (PV) in frontal, limbic, and striatal brain regions and lead to behavioral and neurochemical alterations resembling those found in schizophrenia patients (Beasley et al., 2002; Reynolds et al., 2004; Lewis et al., 2005; Torrey et al., 2005). For example, both maternal immune activation, which produces many behavioral and neurochemical alterations relevant to schizophrenia, and early postnatal immune challenge show alterations in PV-expressing (PV+) interneurons. Mice exposed to PolyI:C *in utero* have decreased PV immunoreactivity in hippocampus and prefrontal cortex in adulthood (Meyer et al., 2008), and administration of lipopolysaccharide (LPS) on postnatal day 7 and 9 to rat pups also produced decreased PV immunoreactivity in the hippocampus (Jenkins et al., 2009). In response to neonatal ventral hippocampal lesion, the inhibitory GABAergic interneuron system

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is also dysregulated, and several studies have shown decreased expression of GAD67 and PV in the PFC (Lipska et al., 2003; Francois et al., 2009). Other studies, however, did not report changes in GAD67 or PV mRNA but did report abnormal responses to D2 stimulation in these interneurons (Tseng et al., 2008). The behavioral alterations produced by gestational methylazoxymethanol (MAM) exposure are also associated with decreased PV+ interneuron number in the PFC and hippocampus (Penschuck et al., 2006; Lodge et al., 2009). MAM treatment during the period of migration of PV+ interneurons, from the medial ganglionic eminence into cortex, produces offspring that show several schizophrenia-like behaviors, alteration in dopaminergic systems, and selective reductions in PV+ interneurons in the PFC and ventral subiculum (Lodge et al., 2009). Importantly, these animals show clear alterations in lateral inhibition and brain oscillatory activity resembling those found in schizophrenia patients (see Lodge and Grace, 2009 for a recent review). Moreover, reverse translational models using schizophrenia-risk genes such as DISC1, NRG1/ErbB4 and Reelin show selective alterations of PV expression and PV+ interneuron physiology (Hikida et al., 2007; Shen et al., 2008; Ammassari-Teule et al., 2009; Fisahn et al., 2009; Ayhan et al., 2010; Fazzari et al., 2010; Neddens and Buonanno, 2010; Wen et al., 2010). Finally, non-genetic or pharmacological models, such as social isolation rearing also produce a decrease in PV expression when animals reach adulthood (Harte et al., 2007; Schiavone et al., 2009). In summary, several neurodevelopmental models of schizophrenia converge on a sustained dysfunction of the fast-spiking PV+ interneuronal system (summarized in Table 1), which may start early during postnatal development.

This review explores the hypothesis that the dysfunction of this inhibitory interneuronal system in neurodevelopmental animal models results from oxidative stress and highlights the early postnatal development of the PV+ interneuronal system as a sensitive period for such brain redox imbalance.

2. Postnatal development of the PV+ interneuronal system

2.1. Inhibitory neurons and development of gamma oscillations

PV+ interneurons are involved in the generation of gamma oscillations, which regulate working memory and information transmission between cortical areas (Salinas and Sejnowski, 2001; Bartos et al., 2007; Gonzalez-Burgos and Lewis, 2008; Roopun et al., 2008; Cardin et al., 2009; Sohal et al., 2009; Uhlhaas et al., 2010). Alterations in brain oscillatory activity are a hallmark of schizophrenia pathophysiology, where derangements in both resting and evoked oscillatory activity are consistently found (Uhlhaas and Singer, 2010). Recent human data show that resting-state and task-related gamma-oscillatory activity emerges during early childhood and that temporal coordination by neural synchrony continues to mature until early adulthood (Uhlhaas et al., 2009, 2010). Additionally, adult levels of performance in delayed response tasks emerge relatively late in the postnatal development of primates (Alexander and Goldman, 1978) and rodents (Bachevalier and Beauregard, 1993; Cobb et al., 1995; de Lecea et al., 1995; Xu et al., 2010). The functional maturation of oscillatory activity and performance in delayed tasks appears to occur concomitantly with PV+ interneuron maturation (Wilson et al., 1994; Rao et al., 2000; Doischer et al., 2008). Thus, the protracted development of the PV+ interneuronal system may constitute a sensitive period where environmental derangements can lead to permanent alterations of inhibitory circuitry, as observed in schizophrenia (Behrens and Sejnowski, 2009).

Although great progress has been made toward the understanding of both the process of postnatal maturation of excitatory networks and the mechanisms underlying the activity-dependent modification of excitatory synapses in principal neurons, understanding of the maturation of inhibitory (GABAergic) circuits has emerged only recently. Unlike principal (excitatory) neurons, which have a relatively conserved set of characteristics, inhibitory interneurons include multiple phenotypes that vary in morphology, physiology and neurochemistry, and represent only 20–30% of neurons in cortex. Due to diversity, low numbers, and the relatively late and activity-dependent maturation of inhibitory neurons, it has been difficult to delineate the transcriptional control of their postnatal maturation.

2.2. Role of inhibition in the development of cortical circuitry

GABAergic interneurons profoundly affect the postnatal development of cortical circuitry (Cobb et al., 1995; Pouille and Scanziani, 2001). These effects are exerted by several interneuron subtypes that have distinct electrophysiological and morphological features, and have different synaptic targets (Kawaguchi, 1993; Krimer and Goldman-Rakic, 2001). In cortex, the different subtypes of GABAergic interneurons were originally classified by their expression of the calcium-binding proteins PV, calretinin, or calbindin (Conde et al., 1994; Cauli et al., 1997). Recently, a more accurate classification through expression of several peptides suggests that most inhibitory interneurons in cortex can also be classified by their expression of PV, somatostatin, and vasointestinal peptide (Xu et al., 2010).

Convergent evidence suggests that contributions from both genes and neural activity affect the development of brain function, and that a correct balance between excitation and inhibition throughout the period of postnatal development is fundamental for the correct development of functional networks leading to the mature brain. In the immature neocortex, inhibitory interneurons generate excitatory depolarizing potentials that are important for the early development of the neural networks (Owens et al., 1999). At the end of the first postnatal week in rodents, this depolarizing activity is switched to inhibition upon expression of the potassium/chloride transporter KCC2 in the postsynaptic neuron (Rivera et al., 1999).

During postnatal development, activity-dependent regulation of gene expression is a major means of remodeling inhibitory networks through experiences (reviewed in Sun, 2007). Starting at the end of the 1st postnatal week in rodents, inhibitory networks play a crucial role in experience-dependent refinement of neural networks that last through week 4 (and beyond, depending on the cortical region Lema Tome et al., 2008; Huang, 2009). During this period, cortical inhibition is fundamental to the formation of critical periods for sensory plasticity (Hensch et al., 1998).

Alterations in GAD67 (the main enzyme responsible for GABA synthesis in cortex) and GABA levels profoundly influence interneuron axon growth and synapse formation during the postnatal development of inhibitory circuits (reviewed in Huang, 2009). Among all inhibitory neurons in cortex, the last to mature is the subtype of PV+ inhibitory neurons in rodents, human and non-human primates (Grateron et al., 2003; Lewis et al., 2004; Hensch, 2005). GABA in these neurons was shown to act beyond inhibitory transmission in the juvenile and adolescent brain, regulating the maturation of inhibitory synapses and innervation patterns (Huang, 2009).

2.3. Developmental trajectory of PV+ interneurons: fine tuning the network

In mice, the maturational process of PV+ interneurons does not start until the end of the 1st postnatal week (de Lecea et al., 1995;