

receptor configuration and promotes behavior that could threaten health or social interactions.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/318/5856/1642/DC1

Materials and Methods

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14 May 2007; accepted 9 October 2007

10.1126/science.1145044

Ketamine-Induced Loss of Phenotype of Fast-Spiking Interneurons Is Mediated by NADPH-Oxidase

M. Margarita Behrens,* Sameh S. Ali, Diep N. Dao, Jacinta Lucero, Grigoriy Shekhtman, Kevin L. Quick, Laura L. Dugan*

Abuse of the dissociative anesthetic ketamine can lead to a syndrome indistinguishable from schizophrenia. In animals, repetitive exposure to this *N*-methyl-D-aspartate-receptor antagonist induces the dysfunction of a subset of cortical fast-spiking inhibitory interneurons, with loss of expression of parvalbumin and the γ -aminobutyric acid-producing enzyme GAD67. We show here that exposure of mice to ketamine induced a persistent increase in brain superoxide due to activation in neurons of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Decreasing superoxide production prevented the effects of ketamine on inhibitory interneurons in the prefrontal cortex. These results suggest that NADPH oxidase may represent a novel target for the treatment of ketamine-induced psychosis.

The *N*-methyl-D-aspartate (NMDA)-receptor (NMDA-R) hypofunction theory of schizophrenia proposes that the effects of NMDA-R antagonists, such as phencyclidine (PCP) and ketamine, produce symptoms of schizophrenia in healthy humans because of specific effects on inhibitory circuits that lead to disinhibition of neurotransmitter systems (1). Disinhibition of glutamatergic activity, resulting in increased excitatory transmission, was confirmed in the prefrontal cortex (PFC) of rodents and non-human primates (2). However, after prolonged exposure, the increased excitatory neurotransmission is followed by a depression of brain activity (3) that occurs through an unknown mechanism.

Derangements of γ -aminobutyric acid (GABA)-mediated systems in schizophrenia have been consistently observed in postmortem tissue (4).

Initial in situ hybridization studies showed reduced expression of GAD67, the main isoform synthesizing GABA in brain (5). Subsequent studies showed also that the expression of the calcium-binding protein parvalbumin (PV) was reduced in postmortem samples (6, 7). Finally, NMDA-R antagonists also induce a decrease in PV expression (8, 9). This apparent "loss of GABAergic phenotype" in PV-containing interneurons led to the suggestion that dysfunction of these fast-spiking inhibitory interneurons may be a core feature of the disease (10).

PV interneurons are involved in the generation of gamma oscillations responsible for temporal-encoding and storage or recall of information required for working memory (11). These interneurons receive the largest glutamatergic input among all GABA-releasing neurons in cortex (12) and are highly sensitive to NMDA-R antagonists (13), a feature that may be related to the role played by NMDA-Rs in the control of basal synaptic activation in these interneurons (14).

We previously showed that primary cortical neuronal cultures respond to NMDA-R antago-

nists with a reversible loss of GAD67 and PV in PV interneurons (15). These neuronal cultures contain about 10 to 20% GABAergic neurons, of which 50% are PV interneurons (15), and show spontaneous glutamatergic and GABAergic activity (16, 17). We hypothesized that if the initial disinhibition of excitatory transmission produced by NMDA-R antagonists observed in vivo also occurred in cultured cortical neurons, then bypassing the need for GABA production by adding a γ -aminobutyric acid type A GABA_A agonist should prevent NMDA-R antagonist-mediated effects (18). Exposure to the GABA agonist muscimol prevented ketamine-mediated decrease in PV and GAD67 in PV interneurons (Fig. 1 and fig. S1), which suggested that loss of an inhibitory input to excitatory neurons, the main neuronal subpopulation in these cultures, is involved in the subsequent loss of phenotype of PV interneurons.

A rapid increase in reactive oxygen species (ROS) occurs in vitro (19), and in vivo (20) after exposure to NMDA-R antagonists, which indicates increased oxidative stress. However, what mechanism initiates this increase is not clear. The recent demonstration of expression of the superoxide-producing enzyme, reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in hippocampus (21) led us to test the possibility that disinhibition of neurotransmission by NMDA-R antagonists leads to increased NADPH oxidase activity. We measured the oxidation product of dihydroethidium (DHE) by confocal microscopy and analyzed the levels of superoxide production in cultured neurons after prolonged exposure to low concentrations of ketamine. A significant increase in neuronal superoxide production was observed after 24 hours' exposure to 0.5 μ M ketamine, which was prevented by muscimol (Fig. 1). The increase in superoxide in response to ketamine was not restricted to PV interneurons (Fig. 1B), which suggested that activation of the enzyme(s) producing superoxide occurs throughout cortical neurons. We next determined whether the increase in superoxide was involved in the loss of GABAergic phe-

Department of Medicine, Division of Geriatric Medicine, University of California San Diego, La Jolla, CA 92093-0746, USA.

*To whom correspondence should be addressed. E-mail: mbehrens@ucsd.edu (M.M.B.); ladugan@ucsd.edu (L.L.D.)

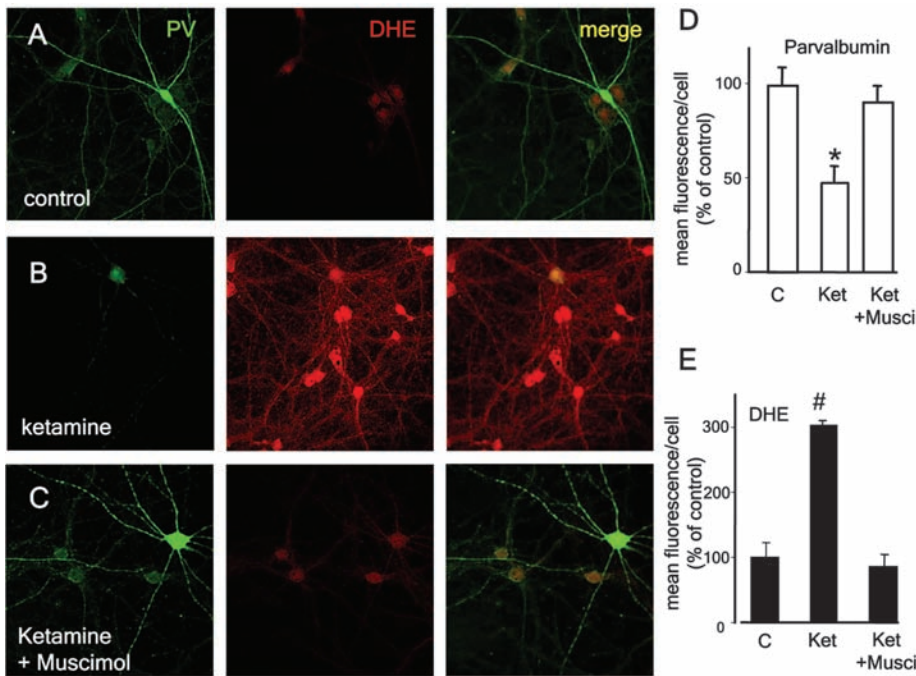


Fig. 1. Ketamine exposure in primary neuronal cultures increases superoxide production and induces the loss of PV immunoreactivity. Neuronal cultures were treated with ketamine (0.5 μ M) for 24 hours as described (15). DHE (1 μ g/ml) was added during the last hour of treatment. (A to C) Fluorescence confocal images of representative fields depicting a PV interneuron and surrounding neurons treated in the absence (control) or presence of ketamine, and in the presence of ketamine and muscimol (10 μ M). Quantification of (D) PV fluorescence, and (E) oxidized DHE. Significant when compared with control at $*P < 0.001$ by analysis of variance (ANOVA) followed by Tukey's test; $n = 5$ experiments per condition. Data are means \pm SEM.

notype of PV interneurons. Indeed, these effects of ketamine were prevented by cotreatment with a carboxyfullerene-based superoxide dismutase (SOD)-mimetic (C_3) (22) (Fig. 2, A and B).

To determine whether the activity of NADPH oxidase is involved in the ketamine-mediated increase in superoxide, we used the inhibitor apocynin (4-hydroxy-3-methoxy-acetophenone) (23). When cultures were exposed to ketamine in the presence of apocynin (at 0.5 mM), superoxide production was significantly reduced (Fig. 2A), and the loss of PV and GAD67 immunoreactivity in PV interneurons was prevented (Fig. 2B). Furthermore, this ketamine treatment increased significantly the expression of the NADPH oxidase subunit Nox2 in neurons (fig. S2).

NADPH oxidase subunits Nox2 and Nox4 are the main core-subunits expressed in forebrain (21). Nox2 is the isoform expressed in phagocytes and requires the membrane protein p22^{phox}, as well as a series of cytosolic proteins involved in its priming and activation. Bacterial infection and inflammation are known activators of Nox2. Nox4 is also dependent on p22^{phox} for activity, but seems to be a constitutive enzyme not requiring activation by cytosolic components. To determine whether ketamine induces NADPH oxidase in vivo, we used a subchronic regimen that consisted of intraperitoneal injections of ketamine (30 mg/kg on two consecutive days) to male C57BL/6 mice, followed by brain dissection 18 hours later. Although the acute effects of ketamine are not detected by this regimen, such

treatment permits the analysis of events that follow the initial disinhibition of the circuitry. We observed a significant increase in the expression of Nox2 and p22^{phox} (Fig. 3A), but not Nox4 (fig. S3C), in membrane preparations from cortex after ketamine treatment. This increase in protein levels was accompanied by an increase in NADPH oxidase activity in synaptosomes isolated from cortex of ketamine-treated animals (Fig. 3B), which suggested that the active enzyme was present at synapses. The increased oxidase activity in synaptosomes was inhibited in vitro by apocynin (Fig. 3B), which confirmed that the main oxidase isoform induced by ketamine in brain is Nox2. Metabolic activities of synaptosomal mitochondria were not affected by the treatment (fig. S3, A and B).

To assess the role of NADPH oxidase activation and superoxide production on PV interneurons, we characterized these interneurons in mouse PFC and analyzed the effects of the 2-day ketamine regimen on PV and GAD67 immunoreactivity. Ketamine induced a significant reduction in immunoreactivity for both proteins in PV interneurons (Fig. 4, A and C), which confirmed that GAD67 decreases in the same subset of interneurons. Moreover, this treatment produced a widespread increase in superoxide (Fig. 4, B and D), which was prevented when animals were pretreated with the NADPH oxidase inhibitor apocynin (5 mg/kg per day) for 1 week in the drinking water, or with the SOD-mimetic C_3 for 1 month (1.0 mg/kg per day, Alzet minipumps). Both treat-

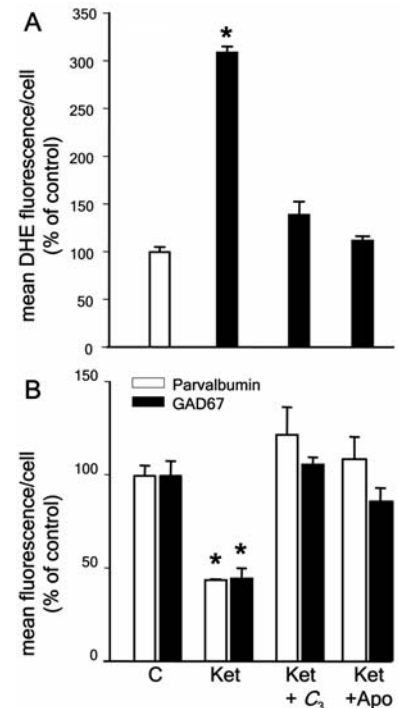


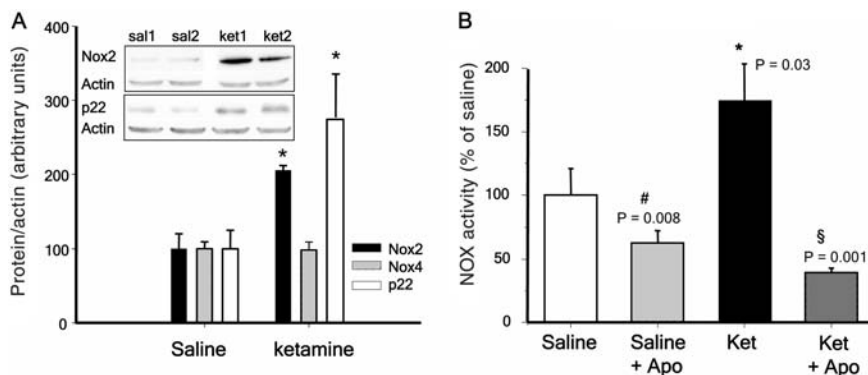
Fig. 2. Removal of superoxide or inhibition of NADPH oxidase activation prevents superoxide increase and reduction of PV and GAD67 in PV interneurons in culture. Cultures were treated with ketamine as in Fig. 1 in the absence or presence of the carboxyfullerene-based SOD-mimetic C_3 (20 μ M) or the NADPH oxidase inhibitor apocynin (0.5 mM). Quantification (A) of oxidized DHE fluorescence, and (B) of PV and GAD67 fluorescence in PV interneurons. Significant when compared with control at $*P < 0.05$ by ANOVA followed by Tukey's test; $n = 4$ experiments per condition. Data are means \pm SEM.

ments completely prevented the loss of PV immunoreactivity in PV interneurons (Fig. 4, B and E). Apocynin also prevented the decrease in GAD67 in PV interneurons in the PFC region (fig. S4).

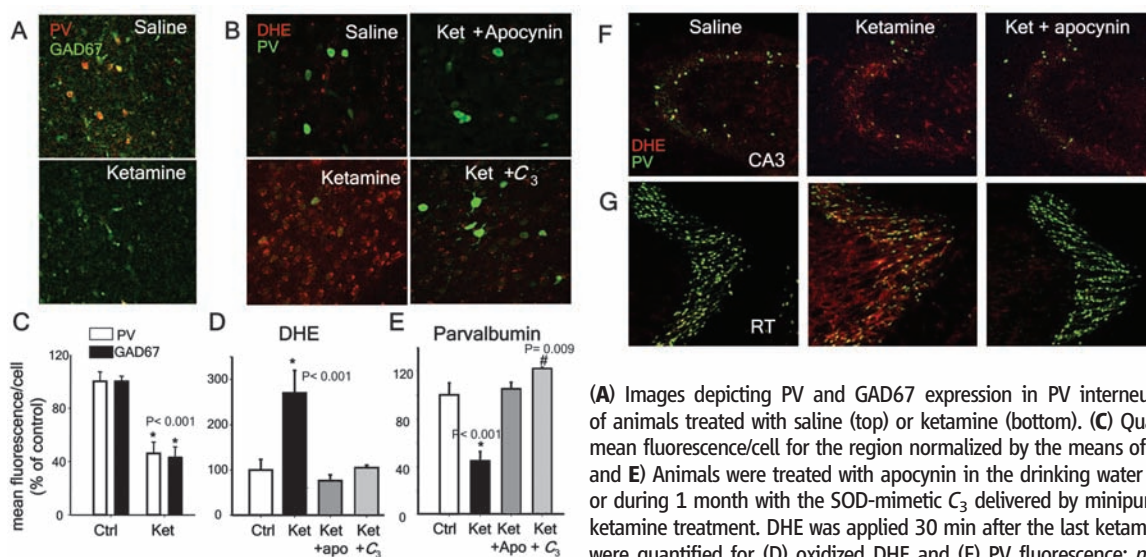
Functional deficits in brain regions other than the PFC, such as hippocampus and thalamus, are known to contribute to schizophrenia symptoms (24, 25). We observed substantial increases in superoxide in several brain regions in addition to the PFC, including CA3 in the hippocampus and the reticular nucleus of the thalamus (Fig. 4, F and G) which suggested that increased NADPH oxidase activity occurs throughout the brain after drug exposure.

Regulatory redox sites have been found in many proteins that are involved in glutamatergic neurotransmission. These include the NMDA receptor itself, in which the oxidation status of a specific redox site on NR2A subunits (from the second class of NMDA receptor subunits) regulates the physiological activity of the receptor (26–29).

Although it is not clear whether the dysfunction of PV interneurons is a cause or consequence of the disease, and extrapolation from the NMDA-R antagonist model to schizophrenia is highly speculative, it is possible that prolonged inactivation of



synaptosomal preparations from animals treated with ketamine as in (A). This activity was inhibited by apocynin. Values of NADPH-induced oxygen consumption (nmol O₂/mg protein per min) were 4.67 ± 0.98, control; 7.9 ± 1.8, ketamine (*n* = four animals per condition). Data are means ± SEM.



is indicated by asterisk and #. (F and G) Confocal images of PV-stained sections depicting the increase in DHE oxidation in (F) hippocampal CA3 region and (G) the reticular nucleus of the thalamus induced by the 2-day ketamine treatment, and its prevention by pretreatment of animals with apocynin in the drinking water.

NMDA-Rs in PV interneurons, due to blockade by antagonists, or more physiologically, by NADPH oxidase-dependent oxidation, leads to a “misinterpretation” of the lack of signal through these receptors as decreased glutamatergic transmission. This, in turn, could be the signal that initiates processes resulting in reduced expression of GABAergic markers and loss of inhibitory capacity in PV interneurons, finally leading to a chronically decreased inhibitory tone in cortex. Recently, a specific decrease in GAD67 and NR2A was observed in a subpopulation of GABAergic interneurons in schizophrenic postmortem tissue (30).

In summary, we hypothesize that NADPH oxidase may be a contributor to oxidative mechanisms involved not only in the psychotomimetic effects of NMDA-R antagonists, but also in schizophrenia and other processes involving increased oxidative stress in the brain. Further understanding of mechanisms underlying activation or induction of brain NADPH oxidase may provide a completely new avenue for drug discovery aimed at the treatment of psychosis and cognitive deficits.

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- We thank M. B. Kennedy, A. Kuspa, W. F. Loomis, and B. Conti for their insightful comments. This work was supported by The Larry Hillblom Endowment (L.L.D.) and by NARSAD (M.M.B.).

Supporting Online Material

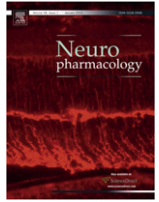
www.sciencemag.org/cgi/content/full/318/5856/1645/DC1
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19 July 2007; accepted 1 November 2007
10.1126/science.1148045



Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

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

Susan B. Powell^b, Terrence J. Sejnowski^{a,c}, M. Margarita Behrens^{a,*}

^a Howard Hughes Medical Institute, The Salk Institute for Biological Studies, La Jolla, CA 92037, USA

^b Department of Psychiatry, University of California, San Diego, MC0804, La Jolla, CA 92093-0804, USA

^c Division of Biological Sciences, University of California, San Diego, La Jolla, CA 92093, USA

ARTICLE INFO

Article history:

Received 3 November 2010

Received in revised form

26 January 2011

Accepted 28 January 2011

Keywords:

Redox

Parvalbumin

Fast-spiking

Gamma oscillations

GABAergic

Interleukin-6

NADPH oxidase

Schizophrenia

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.

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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 is also dysregulated, and several studies have shown decreased

* Corresponding author.

E-mail address: mbehrens@salk.edu (M.M. Behrens).

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 Beaugregard, 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; Doischer et al., 2008; Okaty et al., 2009), although migration is

Table 1

PV+ interneuron alteration and oxidative-stress mechanisms in neurodevelopmental models of schizophrenia.

| | Rodent model | PV expression (protein or mRNA) | Oxidative stress |
|---|--|--|--|
| Risk factor/pathology | | | |
| Social isolation | Post-weaning social isolation rearing | Decrease PV-IR in hippocampus (Harte et al., 2007) and PFC (Schiavone et al., 2009) | Blockade of Nox2 abolishes effect (Schiavone et al., 2009) Increase in other oxidative-stress pathways (e.g., decreased oxidized: reduced GSH ratios, increased SOD) (Moller et al., 2010) |
| Neurodevelopmental NMDA-R hypofunction* | Neonatal NMDA antagonist | Decreased PV-IR in frontal cortex and hippocampus (mice, (Nakatani-Pawlak et al., 2009); rat, (Wang et al., 2008)) exposed to perinatal PCP (PND 7,9,11) Decreased PV-IR in mice exposed to ketamine on PND 7,9,11 (Fig. 1) | Perinatal PCP (PND 2,6,9,12) reduced GSH and altered antioxidants (Radonjic et al., 2010) Oxidative-stress mechanisms of PCP – decreased Bcl-(X)L/Bax ratio (Wang et al., 2003). Absence of perinatal ketamine effects in Nox2-deficient animals (this paper). No data available |
| | Prenatal NMDA antagonist | Decreased PV-IR in medial prefrontal cortex in rats exposed to MK801 prenatally (E15-E18; (Abekawa et al., 2007)) | No data available |
| | Juvenile exposure to PCP | Decreased PV mRNA in mPFC, orbital frontal cortex, nucleus accumbens shell in rats exposed to PCP (PND30–35; (Thomsen et al., 2010)) | No data available |
| Glutathione (GSH) deficit | Postnatal ablation of NMDA-Rs in GABAergic neurons Transitory GSH deficit. GSH deficit produced by BSO (L-buthionine-(S,R)-sulfoximine) from PND 5–16 | Reduced expression of GAD67 and PV (Belforte et al., 2010) Reduced PV-IR in anterior cingulate (Cabungcal et al., 2007) | No data available GSH is a redox regulator and antioxidant |
| Prenatal/Neonatal Immune Activation | Prenatal PolyI:C | Decreased PV-IR in PFC of mice (Meyer et al., 2008) and decreased PV mRNA in PFC of mice via microarray (Smith et al., 2007) | No data available |
| | Neonatal LPS | Decreased PV-IR interneurons in hippocampus of rats (Jenkins et al., 2009) | No data available |
| Developmental hippocampal pathology | Neonatal ventral hippocampal lesion | Decreased GAD67 and PV-IR in PFC adult rats with nVH lesion (Lipska et al., 2003; Francois et al., 2009) | No data available |
| Disruption in neuronal migration | Prenatal MAM | Decreased PV-IR in PFC and hippocampus of rats (Penschuck et al., 2006; Lodge et al., 2009). | No data available |
| Genetic susceptibility/candidate genes | | | |
| Reelin | Homozygous reeler mutants (rl/rl) | Decreased PV-IR in striatum (Marrone et al., 2006) | No data available |
| | Heterozygous reeler mutants (rl/-) | Decreased PV-IR in striatum (Ammassari-Teule et al., 2009) | No data available |
| Impaired glutathione synthesis | Glutamate cysteine ligase modifier (GCLM) KO mice | Decreased PV-IR in ventral hippocampus (VH) (dentate gyrus, CA3) but not dorsal hippocampus (DH) (Steullet et al., 2010) | Increased oxidative stress as measured by 8-Oxo-dG in VH but not DH (Steullet et al., 2010) |
| Neuregulin-ErbB4 | ErbB4 KO mice | Decreased PV-IR in hippocampus ((Fisahn et al., 2009; Neddens and Buonanno, 2010) | No data available |
| DISC1 | DN-DISC1 (dominant negative DISC1) mice | Decreased PV-IR in PFC (Hikida et al., 2007); additive effect on reduced PV-IR with PolyI:C on PND 2–6 (Ibi et al., 2010) ^a | No data available |
| | Truncated DISC1 | Decreased PV-IR in hippocampus and displaced PV-IR in PFC (Shen et al., 2008) | No data available |
| | Inducible mutant human DISC1 (hDISC1) | Decreased PV-IR in cortex of mice with hDISC1 expressed during prenatal, postnatal, or both prenatal and postnatal period (Ayhan et al., 2010) | No data available |
| Lisophosphatidic acid 1 receptor (LPA1) | LPA1 KO mice | Decrease PV-IR interneurons in entorhinal cortex (Cunningham et al., 2006) | No data available |
| 22q11 deletion (DiGeorge syndrome) | LgDel mice (carrying hemizygous deletion from <i>Idd</i> to <i>Hira</i> on 22q11) | Decreased PV-IR interneurons in upper and lower cortical layers (Meechan et al., 2009) | No data available |

*Note: similar loss of PV phenotype observed with adult administration of NMDA antagonists (Rujescu et al., 2006; Jenkins et al., 2010; Behrens et al., 2007, 2008; Braun et al., 2007; Sorce et al., 2010). See text for discussion of important differences between developmental versus adult exposure.

Abbreviations: PV-IR, parvalbumin immunoreactivity; DH, dorsal hippocampus; DISC1, disrupted in schizophrenia; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; GSH, glutathione; IR, immunoreactivity; LPA, lisophosphatidic acid 1; LPS, lipopolysaccharide; MAM, methylazoxymethanol acetate; NRG1, neuregulin 1; PND, postnatal day; NMDA *N*-methyl-D-aspartate; Nox2, NADPH oxidase-2; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; PFC, prefrontal cortex; pNM, perinatal NMDA antagonist; PCP, phencyclidine; PV, parvalbumin; ROS, reactive oxygen species; SI, social isolation rearing; SOD, superoxide dismutase; VH, ventral hippocampus.

^a No effect found with either PolyI:C or DN-DISC1 alone in this experiment.

complete by around embryonic day 15–17 (Tanaka et al., 2006; Liodis et al., 2007; Wang et al., 2010). What prevents these neurons from maturing until postnatal day 5 (P5) is not known. At around P5, these cells start responding to GABA and glutamate transmission (Sauer and Bartos, 2010) and by P7 they start expressing PV (de Lecea et al., 1995). Throughout the next 3 weeks they slowly mature into fast-spiking inhibitory neurons (Doischer et al., 2008; Okaty et al., 2009; Goldberg et al., 2010). This period of maturation occurs concomitantly with a striking transcriptional change (Okaty et al., 2009; Goldberg et al., 2010) in which most of the genes characteristically expressed in mature PV+ interneurons are turned on in an orchestrated fashion between the 2nd and 4th postnatal weeks, coinciding with their electrophysiological maturation (Doischer et al., 2008; Okaty et al., 2009).

Among all interneuron subtypes, PV+ interneurons receive the highest number of glutamatergic synapses from thalamic afferents in the adult rodent brain (Gulyas et al., 1999). These afferents, by contacting both pyramidal and inhibitory neurons, ensure the correct timing of cortical excitation by local feedforward inhibition (Hull and Scanziani, 2007). Glutamatergic neurotransmission preferentially activates Ca²⁺ permeable AMPA-type glutamate receptors on mature PV+ interneurons (Goldberg et al., 2003; Wang and Gao, 2010). However, Ca²⁺ AMPA-mediated currents develop slowly during postnatal maturation, with most immature PV+ interneurons expressing Ca²⁺ impermeable AMPA receptors (Wang and Gao, 2010). On the other hand, the expression and function of NMDA-Rs in PV+ interneurons changes during postnatal development, with high levels being expressed early during postnatal development and profound functional changes occurring during adolescence (Boctor and Ferguson, 2009; Wang and Gao, 2009). Furthermore, confirming our results on developing PV+ interneurons *in vitro* (Kinney et al., 2006), recent results show that GluN2 (NR2) subunits undergo a developmental switch early during postnatal development in PV+ interneurons, and that activity of NMDA receptors in these neurons is fundamental for their maturational process *in vivo* (Zhang and Sun, 2010). This high NMDA/AMPA ratio may make PV+ interneurons extremely sensitive to alterations in NMDA-mediated transmission during their maturational phase.

Thus, it is possible to postulate that environmental inputs that alter the orchestrated process of PV+ interneuron maturation could have profound consequences at the level of experience-dependent plasticity during brain postnatal development, leading to dysfunctional networks when the system reaches adulthood.

3. Behavioral and neuroanatomical consequences of environmental manipulations during the maturation of PV+ interneurons

3.1. Perinatal NMDA receptor-antagonist exposure

Alteration of glutamatergic transmission, specifically blockade of NMDA receptors during the postnatal period leads to a range of behavioral abnormalities that are relevant to schizophrenia, from enhancement of exploration and increased phencyclidine-induced hyperactivity, mimicking psychomotor agitation, to impaired working memory in the delayed alternation task (reviewed in Mouri et al., 2007). Perinatal NMDA receptor-antagonist exposure also leads to impairments in sensorimotor gating (i.e. prepulse inhibition of acoustic startle response), spatial memory, social interaction behavior, and cognitive flexibility in adulthood (Wang et al., 2003; Mouri et al., 2007; Broberg et al., 2008, 2009; Boctor and Ferguson, 2009). In addition to cognitive deficits typical of schizophrenia, rodents treated postnatally with NMDA receptor antagonists showed higher level of fear exhibited in the elevated plus maze (Wedzony et al., 2008) and impairments in conditioned

fear (Hunt, 2006). A decrease in the number of PV+ interneurons and spine density in the frontal cortex, nucleus accumbens and hippocampus was also shown in both rats (Wang et al., 2008; Boctor and Ferguson, 2009) and mice (Nakatani-Pawlak et al., 2009) exposed to early postnatal NMDA-R blockade when analyzed in adulthood.

Furthermore, direct confirmation of the role of NMDA-R function during postnatal development in the expression of schizophrenia-like behaviors comes from results showing that genetic ablation of these receptors from GABAergic neurons from birth decreases the expression of parvalbumin in PV+ interneurons, produces disinhibition of pyramidal neurons, and leads to schizophrenia-related behaviors when mice reach adulthood (Belforte et al., 2010).

3.2. Post-weaning social isolation

Social isolation rearing of young rodents provides a non-pharmacologic method of inducing long-term alterations reminiscent of several symptoms seen in schizophrenia patients (Geyer et al., 1993; Powell et al., 2002). Rearing animals in social isolation is particularly consequential for species that rely on social contact after being weaned from the mother. Specifically, isolation rearing deprives rodents of social interactions during a developmental period in which play behavior emerges (Einon and Morgan, 1977). Thus, as a consequence of social isolation, animals are deprived of stimuli critical to behavioral and neurobiological development (reviewed in Hall et al., 1998). The lack of early social contact provides a model of the social isolation and social withdrawal which occurs early in the course of schizophrenia and predicts conversion to psychosis in patients at a high risk of developing psychosis (Cannon et al., 2008). Rodents reared in social isolation exhibit profound abnormalities in behavior, drug responses, and neurochemistry compared to animals reared in social groups (Hall et al., 1998; Powell and Geyer, 2002; Powell et al., 2002; Fone and Porkess, 2008). In addition to alterations in striatal dopamine function, isolation-reared animals display abnormalities in the hippocampus and frontal cortex (Del-Bel et al., 2002; Silva-Gomez et al., 2003; Preece et al., 2004; Scaccianoce et al., 2006). Specifically, isolation-reared rodents show abnormal firing of pyramidal cells in the PFC upon dopamine stimulation from VTA neurons (Peters and O'Donnell, 2005), decreased volume of PFC (Silva-Gomez et al., 2003; Day-Wilson et al., 2006), and decreased dendritic arborization in the PFC (Silva-Gomez et al., 2003; Pascual et al., 2006). Particularly relevant is the observation that the decreased dendritic arborization in the PFC occurs as early as 2 weeks post-weaning (Pascual et al., 2006), and that social isolation also induces deficits in PV+ interneurons in the brain (Harte et al., 2007; Schiavone et al., 2009).

Rats reared in social isolation show deficits in prepulse inhibition and slow rates of startle habituation (Weiss and Feldon, 2001; Powell and Geyer, 2002). More recent studies have also shown that several different strains of mice exhibit deficits in PPI when reared in social isolation from weaning (Sakaue et al., 2003; Dai et al., 2004; Varty et al., 2006) but see Pietropaolo et al. (2008). Additionally, isolation-reared rodents also display alterations in anxiety-like behavior (Wright et al., 1991; Da Silva et al., 1996), deficits in fear learning (Weiss et al., 2004; Voikar et al., 2005) and deficits visual learning and memory (e.g., novel object recognition test) (Voikar et al., 2005; Bianchi et al., 2006), and cognitive inflexibility as demonstrated by deficits in reversal learning (Krech et al., 1962; Schrijver and Wurbel, 2001) and extradimensional set-shifting tasks (Schrijver and Wurbel, 2001). Thus, isolation rearing is associated with impaired sensorimotor gating, cognitive inflexibility, reductions in PFC volume and hippocampal synaptic plasticity, loss

of PV+ interneurons, hyperfunction of mesolimbic dopaminergic systems, and hypofunction of mesocortical dopamine. The isolation rearing model shows strikingly similar behavioral and neuroanatomical abnormalities as those observed in the perinatal NMDA-R antagonist model and in schizophrenia.

4. Redox dysregulation during postnatal development leads to enduring loss of parvalbumin expression in PV+ interneurons

4.1. Redox dysregulation in schizophrenia

Several studies have reported an altered oxidative state in schizophrenia patients (reviewed in Do et al., 2009). Glutathione (GSH), responsible for detoxification of reactive oxygen and other radical species, is consistently decreased in cerebrospinal fluid of drug-naïve schizophrenia patients (Browne et al., 2000; Do et al., 2000; Lipska and Weinberger, 2000; Rao et al., 2000), as well as in postmortem tissue (Yao et al., 2006). Polymorphisms in genes coding for enzymes that participate in GSH synthesis have been linked to schizophrenia risk (Tosic et al., 2006; Gysin et al., 2007), and recent results show that genetically compromised GSH synthesis affects the morphological and functional integrity of hippocampal PV+ interneurons (Steullet et al., 2010). Furthermore, results showing that treatment with *N*-acetyl-cysteine, a precursor of GSH, improves negative symptoms, and corrects mismatch negativity in schizophrenia patients, support the idea of a redox imbalance in schizophrenia (Berk et al., 2008; Lavoie et al., 2008; Steullet et al., 2008).

4.2. Redox dysregulation in response to NMDA antagonists

In addition to direct manipulations of the redox pathway, other developmental perturbations have been shown to exert their effects through oxidative-stress mechanisms. Using adult repetitive exposures of mice to NMDA-R antagonists, as a model of schizophrenia pathophysiology, we showed that injections of ketamine on two consecutive days induced an increased oxidative state in brain that was sufficient to produce the loss of phenotype (i.e. loss of GAD67 and parvalbumin expression) of PV+ interneurons and an enduring inhibitory dysfunction in the rodent prelimbic region (Behrens et al., 2007; Zhang et al., 2008). The altered oxidative state produced by ketamine was due to a sustained increase in the proinflammatory cytokine interleukin-6 (IL-6) and activation of the superoxide-producing enzyme NADPH oxidase-2 (Nox2). Ketamine effects were absent in Nox2-deficient and IL-6-deficient animals, confirming the role of the IL-6/Nox2 pathway as mediator of ketamine effects (Behrens et al., 2008). Exposure to other non-subunit selective NMDA-R antagonists such as PCP and MK801 were previously shown to produce a rapid increase in brain reactive oxygen- and nitrogen-species (Zuo et al., 2007; Fejgin et al., 2008). To confirm the specific role of NMDA-R blockade in the induction of oxidative stress, we used an NR2A-preferring antagonist (NVP-AAM007), at concentrations known to preferentially affect NR2A-containing receptors (3 mg/kg) (Fantin et al., 2007), and observed a similar increase in superoxide production as that produced by ketamine (values are means \pm SEM. Ketamine: $68 \pm 10\%$ increase over saline; NVP-AAM007: $62 \pm 9\%$ increase over saline. $F_{(2,9)} = 12.636$, $p < 0.05$). These results strongly support a role of increased oxidative stress in the effects of antagonism of NMDA-Rs in the adult brain. Furthermore, a specific role of Nox2 in the acute effects of ketamine was recently shown: using Nox2-deficient mice, Sorce et al. (2010) demonstrated the requirement of this superoxide-producing enzyme in the effects of ketamine, suggesting that even the acute propsychotic effects of NMDA-R

antagonists are due to their ability to activate Nox2 and thus produce a redox imbalance in brain.

4.3. Redox dysregulation during development

Increased oxidative-stress mechanisms during development are hypothesized to be involved in the origin of schizophrenia pathophysiology. Acute decrease in antioxidant capacity during early postnatal periods in rodents, as well as genetic deficiency in GSH produces a loss in PV+ interneurons and induces cognitive derangements relevant to the disease (Cabungcal et al., 2007; Steullet et al., 2010. Summarized in Table 1). Furthermore, genetic dysregulation of glutathione synthesis predicts the alteration in thiol redox status in schizophrenia patients (Gysin et al., 2010). Patients showing high-risk glutamate cysteine ligase, catalytic subunit (GCLC) genotypes had reduced fibroblast production of GSH, decreased total cysteine plasma levels, and increased levels of Cystine. Increased levels of plasma free serine, glutamine, citrulline, and arginine were also observed in the high-risk genotype.

Accumulating evidence shows that embryonic and perinatal NMDA-R antagonist exposures, contrary to the reversible effects observed in adults (Behrens et al., 2008), can produce the loss of PV+ interneurons in several regions when animals reach adulthood (Fig 1) and persistent behavioral and neurochemical deficits (Sircar and Rudy, 1998; Wiley et al., 2003; Andersen and Pouzet, 2004; Stefani and Moghaddam, 2005; Wang et al., 2008; Boctor and Ferguson, 2009; du Bois et al., 2009; Nakatani-Pawlak et al., 2009). Oxidative mechanisms in this model were previously suggested by results showing that antioxidants can prevent the appearance of behavioral disruptions in adult animals that were treated with phencyclidine during the perinatal period (Wang et al., 2003).

4.4. Nox2 mediates effects of perinatal ketamine and social isolation on PV+ interneurons

To test the role of Nox2 in the loss of PV+ interneurons in this model, we exposed Nox2-deficient animals and their wild type littermates to ketamine (30 mg/kg, SC) on postnatal days 7, 9, and 11,

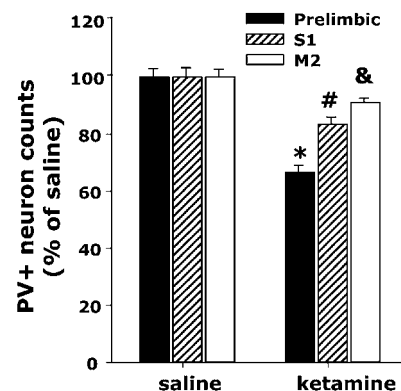


Fig. 1. Perinatal exposure to ketamine reduces the number of PV-expressing interneurons in the adult frontal cortex. Litters from two C57BL/6 females per treatment condition were injected subcutaneously with either saline or ketamine (30 mg/kg) on postnatal days 7, 9, and 11. Males, 5 for each treatment condition, were perfused with 4% paraformaldehyde when they had reached 8 weeks of age, and their brains sliced for floating section immunohistochemistry as described (Behrens et al., 2007). Six consecutive slices encompassing the frontal region were immunostained with Vectastain for detection of parvalbumin using a polyclonal antibody (Swant, Switzerland). Cells in each region were counted as described (Dugan et al., 2009). All cells in the region were counted and total numbers per slice were corrected using Abercrombie's (1946) correction algorithm and normalized to the saline samples. Bar graphs represent means \pm SEM. *,#, & indicates statistical significance with respect to saline on each brain region as assessed by ANOVA followed by Tukey's test ($F_{(1,8)} = 105.351$, $p < 0.05$; $F_{(1,8)} = 25.460$, $p < 0.05$; $F_{(1,8)} = 9.366$, $p = 0.05$).

and counted the PV+ interneuronal population in the prelimbic region when animals had reached adulthood (8 weeks). Nox2-deficiency completely prevented the loss of PV+ interneurons in the prelimbic region. PV-expressing neurons were counted as described in Dugan et al. (2009) and expressed as percent of wild type saline conditions (results are means \pm SEM. Nox2^{+/+}-saline = 100 \pm 5%, Nox2^{+/+}-ketamine = 63 \pm 1.7%; Nox2^{-/-}-saline = 99 \pm 2%, Nox2^{-/-}-ketamine = 97 \pm 3%). A two-way ANOVA revealed a significant effect of treatment ($F_{(1,15)} = 52.10$, $p < 0.001$), genotype ($F_{(1,15)} = 36.62$, $p < 0.001$) and a significant genotype \times treatment interaction ($F_{(1,15)} = 58.71$, $p < 0.001$). Tukey's post hoc analysis revealed a statistically significant difference between Nox2^{+/+}-saline and Nox2^{+/+}-ketamine ($p < 0.001$), and between Nox2^{+/+}-ketamine and Nox2^{-/-}-saline ($p < 0.001$) and between Nox2^{+/+}-ketamine and Nox2^{-/-}-ketamine ($p < 0.001$).

Recent studies have implicated Nox2-dependent oxidative mechanisms in the loss of PV+ interneurons and development of schizophrenia-like behavior in the isolation rearing model (Schivone et al., 2009). Corroborating earlier work (Harte et al., 2007), Schivone et al. (2009) found decreased PV immunoreactivity in the brains of rats reared in social isolation. This loss of PV+ interneurons was associated with elevations in Nox2, and the decrease in PV-staining and deficits in novel object recognition were blocked by treatment with the Nox2 inhibitor apocynin (Schivone et al., 2009). Studies should be done to determine whether other behavioral abnormalities (e.g., disruptions in PPI) can be prevented by treatment with apocynin in this model. Recent studies have shown that isolation rearing is associated with oxidative stress as measured by increased superoxide dismutase, decrease oxidized/reduced glutathione ratio, and increased concentrations of malondialdehyde (Moller et al., 2010). Interestingly, these markers of oxidative stress were all reversed with chronic clozapine administration (Moller et al., 2010).

The wide-spread apoptosis in retrosplenial cortex caused by high doses of NMDA antagonists during the perinatal period had led to the conclusion that the reduced number of PV+ interneurons observed (see Fig 1) was due to their death (Olney et al., 1999; Wang et al., 2003, 2008). To test whether this was the case, we took advantage of a mouse line expressing green fluorescent protein exclusively in PV+ interneurons (G42 line, Chattopadhyaya et al., 2004; Di Cristo et al., 2004) and exposed these animals during the 2nd postnatal week (postnatal days 7, 9, and 11) to ketamine (30 mg/kg, s.c.). Analysis of parvalbumin and GFP co-expression when animals were in their 5–6th week of age showed a similar decrease in PV+ neurons as we had observed in wild type adult animals (Fig 1). However, there was no decrease in GFP-expressing neurons (Fig 2), suggesting that while the cells are still alive their developmental maturation may be affected. As commented above, PV+ interneurons reach maturity at around week 5 (de Lecea et al., 1995; Doischer et al., 2008; Lema Tome et al., 2008; Huang, 2009). The similarity in the results depicted in Figs. 1 and 2 strongly suggest that perinatal ketamine exposures/oxidative-stress mechanisms produce an alteration in the normal development of PV+ interneurons which is already evident during adolescence. Similar results were recently obtained using a mouse line expressing GFP in all GABAergic neurons (Zhang and Sun, 2010). In this study, and using an NR2A-preferring antagonist, the authors show that prolonged blockade of NR2A-containing receptors in vivo during the critical period of plasticity in the barrel cortex produced a decrease in PV expression and an alteration of fast-spiking-mediated IPSCs onto principal neurons.

4.5. Functional alteration in cortical networks

Networks of PV+ interneurons tightly interact with excitatory-neuron firing and affect dynamics of cortical activity (Borgers et al.,

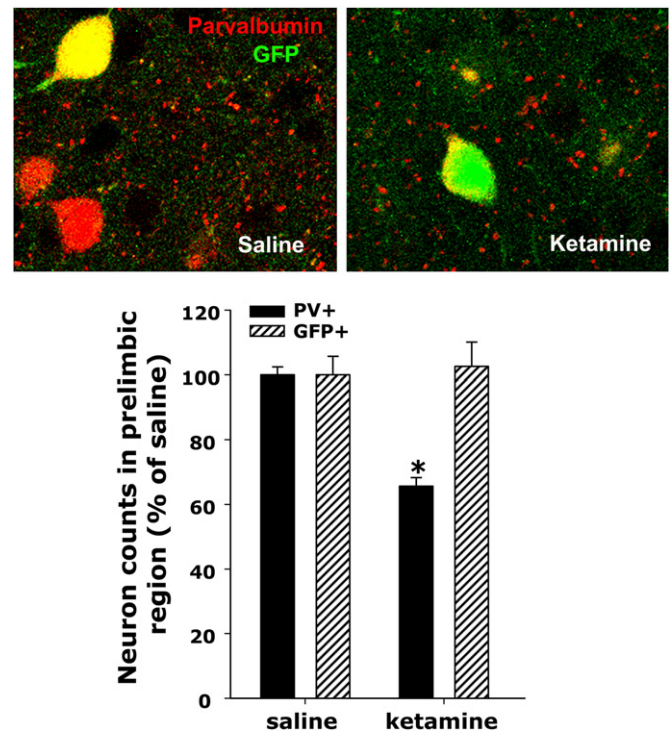


Fig. 2. Loss of PV expression without death of the interneurons. The heterozygous progeny of G42 X C57BL/6 crossings was treated with saline or ketamine during the 2nd postnatal week as described in Fig. 1 and the animals were perfused between the 5th and 6th week of age. The G42 line expresses GFP in approximately 50% of PV+ interneurons (Chattopadhyaya et al., 2004; Di Cristo et al., 2004). (A) Colocalization of GFP and PV was determined by confocal microscopy using a Zeiss Pascal system and AlexaFluor 568 as secondary antibody for detection of PV. (B) The prelimbic region on each slice was imaged across six consecutive slices, and across 16 μ m on the Z axis. Images were then collapsed and the number of cells expressing PV or GFP was counted as described in Fig. 1 and normalized by the mean of the saline controls. As described in Fig. 1, there was a statistically significant decrease in the number of PV-expressing neurons, but there was no decrease in the GFP-expressing population. Since all GFP-expressing neurons were also positive for PV in saline controls, as previously described (Chattopadhyaya et al., 2004; Di Cristo et al., 2004), these results suggest that the PV-interneuronal population is still present in these animals, but the neurons do not express their characteristic marker, parvalbumin. Bar graphs represent means \pm SEM. *indicates statistical significance ($p < 0.005$) with respect to saline as determined by ANOVA ($F_{(3,12)} = 12.278$, $p < 0.001$) followed by Tukey's pos hoc test.

2008; Tiesinga and Sejnowski, 2009). Each PV-interneuron makes contacts with many principal neurons, and dysfunction of a single interneuron may desynchronize a large portion of the local network and disrupt cortical information processing. Thus, when the PV+ interneuronal system contains a proportion of cells with altered electrophysiological characteristics, a functional consequence may be altered sensory processing and cognitive dysfunction as observed in schizophrenia (Javitt, 2009; Uhlhaas and Singer, 2010). Support for this hypothesis comes from recent data showing that decreased expression of parvalbumin in synaptic terminals leads to increased asynchronous GABA release from PV+ interneurons (Manseau et al., 2010). This asynchronous GABA release in turn reduces the ability of principal neurons to integrate incoming stimuli into precise firing.

5. Discussion

In summary, there is converging genetic, pharmacological and non-pharmacological evidence that oxidative stress in the early postnatal period affects the normal neurodevelopment of PV+ interneurons and increases the risk of schizophrenia in adulthood.

The mechanism by which oxidative stress leads to the enduring dysfunction of PV⁺ interneurons is unknown. As we previously suggested, acute redox imbalances in brain may affect several neurotransmitter systems, with the glutamatergic synapse being particularly sensitive to oxidative stress (Behrens and Sejnowski, 2009). However glutamatergic synapses are found on many types of cortical neurons, but only the PV⁺ interneurons show redox sensitivity during postnatal maturation. This increased sensitivity could be due to the fundamental role that glutamatergic transmission has on the maturation of these interneurons. Alternatively, redox-mediated changes in transcription activity, per se, may affect the orchestrated maturational process of PV⁺ interneurons. Under physiological conditions, nuclear antioxidants (specifically GSH) are critical for maintaining the reducing environment needed to ensure proper gene transcription (Green et al., 2006). A number of transcription factors contain redox-sensitive cysteine residues at their DNA-binding sites (Haddad, 2002), and in most cases, oxidation of these proteins inhibits their DNA-binding activities (Turpaev, 2002). The transcriptional activation responsible for PV⁺ interneuronal maturation occurring during the early postnatal period may be in fact what makes this interneuronal system so highly redox sensitive. Increased oxidative stress during this postnatal period may halt or alter the maturational process, and in this way lead to a dysfunctional PV⁺ interneuronal network in adulthood. Detailed understanding of the mechanisms controlling the maturation program of PV⁺ interneurons and how they are affected by redox dysregulation will shed light into the mechanisms underlying experience-dependent maturation of inhibition, and may unravel the origins of schizophrenia. Moreover, detailed understanding of the electrophysiological consequences that alteration of PV⁺ interneuron maturation has at the network level, will give insights into the derangements in oscillatory activity observed at the systems level in schizophrenia patients.

PV-expressing interneurons first appear in the human cortex postnatally, between the 3rd and the 5th month of age (Reynolds and Beasley, 2001; Grateron et al., 2003). However, the time course of their maturation is not known. In other species, the period of maturation of PV⁺ interneuronal circuits in cortex ends at different times during postnatal development, with somatosensory and visual cortex maturing first and prefrontal regions maturing last (Hensch, 2005). In rodent cortex, this maturation coincides with the appearance of $\alpha 1$ GABA(A) containing receptors (Fritschy et al., 1994), which are characteristic of mature PV-synaptic contacts (Klausberger et al., 2002). The development of synchronized oscillatory activity also follows the same time course as the maturation of PV⁺ interneurons in each cortical region (Doischer et al., 2008). Based on postnatal changes in synchronization of oscillatory activity (Uhlhaas et al., 2009, 2010) and the switch in GABA(A) receptor subunit expression in primate frontal cortex (Hashimoto et al., 2009), the period of maturation of the cortical PV⁺ interneuronal system in this brain region could range from childhood to early adulthood in humans. Thus, a better understanding of the sensitive periods to oxidative-stress mechanisms that alter the development of the PV⁺ interneuronal system may shed light on efforts at early intervention for psychosis.

The prognosis of schizophrenia is much improved when the psychotic symptoms are treated early in the course of the illness (Browne et al., 2000; Wyatt and Henter, 2001; Rosen et al., 2002; Melle et al., 2008). Indeed, prolonged periods of untreated psychosis are associated with an unfavorable treatment outcome and reduced quality of life (Wyatt and Henter, 2001), (Browne et al., 2000). If the emergence of schizophrenia is associated with a prolonged oxidative state in the brain, treatment of oxidative stress may be an effective early intervention. Indeed, several studies have shown that blockade of redox pathways prevents the behavioral

and neurochemical effects of neonatal NMDA-R antagonists (Wang et al., 2003) and isolation rearing (Schiavone et al., 2009; Moller et al., 2010). The GABAergic inhibitory system, specifically the PV⁺ interneurons, may be uniquely sensitive to various environmental perturbations during early development and thus may be uniquely responsive to early interventions.

6. Conclusions

Pathophysiological studies of schizophrenia are beginning to converge on a specific set of inhibitory neurons, the PV-immunoreactive fast-spiking interneurons, which are critically positioned to modulate higher order cognition, and which are clearly implicated in schizophrenia. However, when and how the selective dysfunction of these neurons occurs has not yet been established. Our results using adult and perinatal exposures to NMDA-R antagonist suggest that activation of the IL-6/Nox2 pathway and subsequent increase in oxidative stress may be responsible for the dysfunction and loss of PV⁺ interneurons. Support for this hypothesis comes from recent data showing that activation of this same oxidative pathway is responsible for the neurochemical and behavioral outcomes in the isolation rearing model. Together, these results point to the period between the 2nd and 4th postnatal week in rodents as a sensitive period where environmental perturbations, by producing increased oxidative stress in brain, may indelibly affect the maturation of the PV-inhibitory circuitry and increase the risk for the development of mental diseases in adulthood.

This interneuron-development hypothesis suggests novel therapeutic interventions for treating schizophrenia, such as brain-targeted anti-IL-6/Nox2 strategies during postnatal manipulations, which could be tested in model systems to determine whether psychosis and cognitive deficits in early adulthood can be prevented.

Acknowledgments

We were supported by the National Institute of Mental Health grant MH091407-01 (SBP and MMB), the Howard Hughes Medical Institute (TJS), and NARSAD (MMB). We would like to thank Dr. Mark Geyer for helpful discussions.

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