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Cortical disinhibition in the neonatal ventral hippocampal lesion model of schizophrenia: New vistas on possible therapeutic approaches

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ABSTRACT

The neonatal ventral hippocampal lesion (NVHL) model of schizophrenia has been extensively used in many laboratories over the past couple of decades. With more than 120 publications from over 15 research groups, this developmental model yields a number of schizophrenia-relevant behavioral, neurochemical and electrophysiological deficits. An important aspect of this model is the delayed emergence of alterations, typically during adolescence despite the manipulation that causes them having been performed during the first postnatal week. Such delayed timing reflects the periadolescent onset of schizophrenia symptoms and may be related to the protracted maturation of cortical circuits, affected in both the disease and the NVHL model. Here, I will review the work we have done regarding the maturation of prefrontal cortical-accumbens circuits during adolescence, and how this maturation is affected in rats with a NVHL. One of the principal elements affected in NVHL rats is the dopamine modulation of prefrontal cortical interneurons, and this finding is convergent with data from many other developmental, genetic and pharmacological models. An altered maturation of interneuron function would yield a disinhibited cortex, and this opens the way to novel therapeutic approaches for treatment and even prevention of schizophrenia.

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1. Introduction

Important clues are slowly being revealed about brain changes in schizophrenia, a disorder once described as “the graveyard of pathology” because of the absence of identifying pathological changes. On one hand, the existence of predisposing genes, which had been anticipated for decades, has now been definitely established (Mirnics et al., 2001; Weinberger et al., 2001). On the other hand, several groups have unveiled pathological alterations in post-mortem studies that indicate structural and functional changes in diverse cortical and subcortical

brain regions (Harrison, 2004; Lewis et al., 2004). Despite this wealth of information, a unifying view of pathophysiological mechanisms leading to this devastating disorder is only starting to emerge. Many attempts have been made at establishing a *systems* model of what may go wrong in the brain of those affected with schizophrenia, and these models focused on dopamine (DA) systems, glutamate and gamma-aminobutyric acid (GABA) prefrontal and hippocampal circuits. Each model has indeed advanced our understanding of some aspect of this disease; however, we are still short of an integrative picture identifying critical pathophysiological processes that could eventually lead to new therapeutic approaches.

Animal models of the disease are promising in that regard. The initial approaches at animal research related to schizophrenia pathophysiology were, not surprisingly, pharmacological in nature. The ability of amphetamines to induce psychosis (Snyder, 1973) was in line with the DA hypothesis of schizophrenia. Subsequent developments highlighted

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that while amphetamine psychosis showed little resemblance to schizophrenia, other agents such as phencyclidine caused changes more akin to the disorder (Luby et al., 1959; Javitt & Zukin, 1991). Although these research lines provided important insight, the developmental aspects of schizophrenia were not addressed. Diverse developmental models emerged over the last couple of decades. While all have strengths and weaknesses and it is clear that it is not possible to reproduce all aspects of the disease in a single model, they may provide valuable information related to plausible pathophysiological scenarios. These models range from environment-based manipulations (i.e., raising animals in social isolation (Paulus et al., 1998), prenatal malnutrition or stress (Rehn et al., 2004)) to more aggressive tactics such as impairing cell division during gestation (Flagstad et al., 2004) or lesioning a critical brain area in the early postnatal period (Lipska et al., 1993). One of the most comprehensively studied developmental models is the neonatal ventral hippocampal lesion (NVHL). This manipulation does not reproduce hippocampal changes in schizophrenia, as patients do not present a lesion. However, the absence of proper hippocampal innervation at a critical neurodevelopmental period may have long-term consequences on synaptic connectivity and function of prefrontal cortex (PFC) neural circuits (Tseng et al., 2009). Here, I will review work conducted by us and others using the NVHL model, in which most deficits emerge during adolescence.

2. Adolescent maturation of corticostriatal circuits

The brain regions and neurotransmitter systems implicated in schizophrenia have a protracted postnatal maturation. In the primate PFC, local inhibitory synapses increase connectivity during adolescence, to be pruned in the transition to adult circuitry. This is evidenced by markers of interneuron terminals such as the GABA transporter, or markers of interneuron function such as parvalbumin, showing dramatic changes during adolescence (Anderson et al., 1995; Woo et al., 1997; Erickson & Lewis, 2002). The density of DA fibers, assessed with tyrosine hydroxylase (TH) staining, also increases from the juvenile stage to adolescence to be decreased in the adult monkey (Rosenberg & Lewis, 1994). In rodents, neurochemical assessments also reveal strong changes during adolescence. DA receptors increase in the juvenile PFC, to be pruned during adolescence (Andersen et al., 2000). A developmental change of note during adolescence is the transient increase in D₁ receptor expression in pyramidal neurons projecting to the nucleus accumbens (NA) (Brenhouse et al., 2008). Combined, these data indicate that adolescence is a period in which synaptic connectivity within the PFC becomes refined in rodents and primates alike.

Physiological changes are also present during adolescence in the PFC, with the DA control of cortical neuronal activity showing important modifications. Electrophysiological assessment of the D₁ modulation of NMDA responses in PFC pyramidal neurons revealed that although D₁ agonists enhance NMDA responses in all age groups (Wang & O'Donnell, 2001; Tseng & O'Donnell, 2004), the ability of inducing persistent depolarizations resembling up states by D₁-NMDA co-activation emerges during early adolescence (postnatal day (PD) 40–45) (Tseng & O'Donnell, 2005). This enhanced effect of D₁ receptors during adolescence could be a reflection of the increase in D₁ receptor density (Brenhouse et al., 2008), and could yield a more excitable PFC that may drive risk-taking and exploratory behaviors in this developmental stage.

The modulation of local PFC GABA interneurons by DA also matures during adolescence. In the juvenile PFC, D₁ activation enhances excitability in fast-spiking, parvalbumin-positive interneurons while D₂ agonists exert the opposite effect (Gorelova et al., 2002). During late adolescence (around PD 55), the response of rat fast-spiking interneurons to D₂ activation switches to a strong excitation (Tseng & O'Donnell, 2007a,b; Kroener & Lavin, 2010). Activation of interneurons by D₂ receptors modulates the responses of

pyramidal neurons to cortico-cortical afferent activation in the adult, not juvenile rat (Tseng & O'Donnell, 2007a,b). This change would yield a more effective filtering out of irrelevant information in the adult PFC. Interestingly, the enhanced D₁-NMDA interaction occurs at around PD 45, earlier than the switch in D₂ modulation of interneurons. Although in our study of interneuron modulation by D₂ agonists we did not include any data from adolescent rats, unpublished recordings showed that fast spiking interneurons would make the switch to being excited by a D₂ agonist by PD 50–55. In some cases, two neurons from the same animal would show different modulation: one the immature absence of D₂ excitation and the other one the adult-like excitation by the agonist. This variability suggests that individual neurons and not the animal are making the transition to the adult DA modulation in that age span. This would result in the adolescent period being characterized by an increased excitability of PFC circuits and the recruitment of inhibitory circuits by DA comes online slowly, and therefore may result in poorer performance at some levels and increased risk-taking.

Human studies also reveal maturation of GABA interneuron circuits during adolescence. Interneuron-dependent oscillations that correlate with cognitive performance change during adolescence. In a study of neural synchrony during visual display of Mooney faces, Uhlhaas et al. reported that in children, performance correlates with electroencephalogram synchrony, in adolescents synchrony is affected and performance is low, and in adults synchronization patterns become reorganized with emergence of high-frequency components (Uhlhaas et al., 2009). Thus, cortical activity in the adolescent period may undergo significant rearrangement, yielding the possibility of higher risk for psychiatric disorders.

The NA also shows significant changes during adolescence. Corticoaccumbens synaptic responses are modulated by DA, and the nature of this modulation can be studied in a slice preparation that preserves the PFC and NA. The D₂ agonist quinpirole attenuates PFC-NA synaptic responses in slices from juvenile (PD 23–38) rats and enhances the amplitude of these synaptic responses in slices from late adolescent or young adult rats (PD 50–63). The effect in the adolescent and adult NA involves activation of local GABA interneurons, as it can be blocked by GABA-A antagonists (Benoit-Marand & O'Donnell, 2008). It is remarkable that the modulation of NA response to PFC stimulation by DA changes during adolescence with the acquisition of an upregulation of local fast-spiking, parvalbumin positive interneurons by D₂ receptor activation, as it is also the case in the PFC.

Overall, these findings indicate that the control of PFC and ventral striatal information processing by DA becomes refined during adolescence. Such dramatic changes may confer the adolescent brain with enhanced vulnerability to environmental factors such as stress, and may contribute to unmask preexisting alterations that may not be evident in immature preadolescent circuits. A close look at periadolescent maturation of cortical circuits in normal animals and in disease models is likely to provide important information regarding schizophrenia pathophysiology.

3. The neonatal ventral hippocampal lesion model

An excitotoxic lesion in the ventral hippocampus produced by PD 7–8 yields a number of alterations resembling schizophrenia-relevant phenomena. This model was developed by Barbara Lipska and Daniel Weinberger at the NIMH, and became extensively used in diverse academic settings. A critical feature of this model is the narrow timing window for the lesion to elicit periadolescent onset alterations (Lipska et al., 1993). Similar lesions at different ages do not yield the same cluster of anomalies (Becker et al., 1999). The NVHL model is therefore likely reproducing the effects of diverse insults at a critical developmental stage.

3.1. Behavioral deficits

Rats with a NVHL exhibit a variety of behavioral anomalies that emerge after puberty. Behavioral measures that are thought to be relevant to positive symptoms of schizophrenia include enhanced locomotion (Sams-Dodd et al., 1997; Al-Amin et al., 2001), exaggerated reaction to stress, amphetamines (Lipska et al., 1993; Kato et al., 2000), and non-competing NMDA antagonists (Al-Amin et al., 2001). The negative symptom cluster is reproduced as deficits in social behavior in adult rats (Sams-Dodd et al., 1997; Becker et al., 1999). NVHL rats also present schizophrenia-related cognitive-deficits, including sensorimotor gating deficits revealed with reduced prepulse inhibition (PPI) of the acoustic startle response (Lipska et al., 1995; Swerdlow et al., 1995; Le Pen & Moreau, 2002), latent inhibition (Grecksh et al., 1999), and working memory deficits (Chambers et al., 1996; Moghaddam et al., 1999; Lipska et al., 2002a; Brady et al., 2010). More complex behavioral assessments revealed changes in set-shifting reminiscent of PFC deficits (Brady, 2009), deficits in associative conditioning (Macedo et al., 2008), and cognitive inflexibility (Gruber et al., 2010). In an odor-guided choice task in which DA cells fire rapidly as the rats sample a smell to guide their behavior (Roesch et al., 2007), NVHL rats perform more poorly than controls, in particular when reversal learning was required (Gruber et al., 2010). These data indicate that the NVHL can produce cognitive deficits in adult rats that bear relevance for schizophrenia. In addition, some studies have shown that monkeys with a neonatal hippocampal lesion show abnormal social behaviors at adult ages (Bachevalier et al., 1999; Malkova et al., 2011). Thus, neonatal inactivation of hippocampal activity produces several domains of behavioral deficits that emerge during adolescence.

The NVHL model also reveals increased liability for addictive behaviors. NVHL rats show increased cocaine self-administration (Chambers & Self, 2002), and ethanol intake (Berg et al., 2011). Furthermore, they show enhanced methamphetamine self-administration, but this is only revealed when animals are tested in a progressive ratio paradigm (Brady et al., 2008). NVHL rats also show enhanced behavioral sensitization for nicotine (Berg & Chambers, 2008), alcohol (Conroy et al., 2007) and cocaine (Chambers & Taylor, 2004). If, as suggested, adolescence is a period of enhanced vulnerability for addictive behaviors (Brenhouse et al., 2008), then abnormal adolescent maturation in NVHL rats (and perhaps schizophrenia) could enhance such vulnerability.

3.2. Neurochemical and anatomical changes

NVHL rats exhibit anatomical and neurochemical changes in corticostriatal circuits. In the PFC, there have been reports of reduced BDNF levels (Ashe et al., 2002) and GAD67 mRNA (Lipska et al., 2003; Francois et al., 2009). Also, increases in GABA-A receptor density (Endo et al., 2007) and mRNA expression (Mitchell et al., 2005) have been reported. NVHL rats show increased cortical nitric oxide (NO) and NO synthase levels (Bernstein et al., 1999; Negrete-Diaz et al., 2010), and strong indicators of altered synaptic connectivity in the PFC of NVHL rats are the reported changes in spine density and spine length (Flores et al., 2005; Alquicer et al., 2008), and in dendritic branching (Flores et al., 2005). Many intracellular signaling cascades are altered in adult rats with a NVHL, including ERK1/2, Akt and GSK-3 (Bychkov et al., 2011). In striatal regions, NVHL rats show a decrease in dendritic spine density in the NA (Flores et al., 2005), and reduced D₂ mRNA expression (Lipska et al., 2003; El-Rawas et al., 2009). Also, the DA response to stress is attenuated in the NA (Brake et al., 1999). These findings indicate that cortical and striatal architecture is critically affected in this model, suggesting that corticostriatal function may also be altered. PFC GABA transmission is among the systems impaired in NVHL rats, as revealed by reduced GAD67 mRNA (Lipska et al., 2003) and increased levels of GABA-A receptor subunits (Mitchell et al., 2005).

Most of these deficits emerge during adolescence. Although many studies have tested behavioral and neurochemical endpoints only in

adult rats with NVHL, in some cases a pre-adolescent group was included. When a younger cohort was included, the deficits were observed in adult, not juvenile NVHL rats (Al-Amin et al., 2001; Goto & O'Donnell, 2002). Also, a similar lesion performed in adult rats did not yield the same array of anomalies (El-Rawas et al., 2009). Therefore, this model seems to imply two distinct and critical developmental periods: an early one, when the lesion is made and likely affecting the establishment of synaptic architecture, and a late one during adolescence in which these circuits would normally mature.

3.3. Electrophysiological alterations

Further characterization of DA alterations in the NVHL model was obtained using electrophysiological methods. Electrical stimulation of the ventral tegmental area (VTA), the source of DA innervation to the PFC, results in a suppression of firing in pyramidal neurons in naïve animals (B. L. Lewis & O'Donnell, 2000). In adult NVHL rats, VTA stimulation evoked a dramatic increase in firing (O'Donnell et al., 2002), which can be interpreted as resulting from loss of interneuron activation by DA. VTA stimulation also produces abnormally high cell firing in the NA in adult, not prepubertal NVHL rats (Goto & O'Donnell, 2002), which can also be prevented by haloperidol (Goto & O'Donnell, 2002) or a PFC lesion (Goto & O'Donnell, 2004). The latter finding was interpreted as suggesting that increased NA firing is secondary to abnormal information processing in the PFC in NVHL rats. As these abnormal responses are observed only after adolescence, periadolescent maturation of PFC-NA circuits may be affected by the absence of proper hippocampal innervation during early stages of development.

The increased PFC cell firing evoked by VTA stimulation suggests a state of hyperexcitability in NVHL rats that could be explained by abnormal modulation of PFC interneurons. Indeed, fast-spiking interneurons in the medial PFC of adult NVHL rats do not show the excitation by D₂ agonists (Tseng et al., 2008). The abnormal interneuron maturation in the PFC of NVHL rats was also evident in the loss of a GABA component in the D₂ modulation of cortico-cortical synaptic responses (Tseng et al., 2008). Therefore, absence of proper hippocampal inputs to the PFC during early development may result in abnormal circuits, which would not initially yield overt dysfunction. Only when periadolescent maturation and refining of the DA modulation of PFC interneurons occur, a failed local inhibition would become evident and yield a disinhibited cortex. Indeed, in a choice task that involves DA activation, twice as many pyramidal neurons in the medial PFC increased firing in NVHL rats compared to controls at the time DA cells fire in bursts (Gruber et al., 2010). Furthermore, interneuron-dependent high frequency oscillations emerged during the odor sampling component of the task in controls but not in NVHL rats (Gruber et al., 2010). Auditory-evoked high frequency oscillations, which are also interneuron dependent, are affected in NVHL rats (Vohs et al., 2010). Thus, it is conceivable that abnormal interneurons are among the key elements underscoring behavioral, neurochemical, and electrophysiological anomalies emerging during adolescence in animals with a neonatal hippocampal lesion.

3.4. Effects of antipsychotic medication

Whenever tested, antipsychotic treatment reverses behavioral and electrophysiological anomalies in NVHL rats. The enhanced locomotor activity is reversed with haloperidol and clozapine (Lipska & Weinberger, 1994; Le Pen & Moreau, 2002), as well as with low doses of risperidone (Richtand et al., 2006). Haloperidol and clozapine attenuate non-competing NMDA antagonist-induced hyperlocomotion (Al-Amin et al., 2000), and the increase in NA cell firing with VTA stimulation is abolished after haloperidol treatment (Goto & O'Donnell, 2002). Clozapine, olanzapine and risperidone reverse PPI deficits in NVHL rats (Le Pen & Moreau, 2002). Thus, both classical and atypical antipsychotic drugs

reverse some aspects of the NVHL model, typically on measures that could be related to positive symptoms. On the cognitive deficit realm, these drugs do not seem to have a strong effect, but a recent study showed an attenuation of reversal learning deficits of a novel non-DA agent (a mGluR2/3 agonist) (Gruber et al., 2010). The NVHL rat model is therefore suitable for testing novel compounds that are being designed to target a disinhibited cortex.

4. Cortical disinhibition in schizophrenia

4.1. Altered interneurons in schizophrenia

Several postmortem studies highlight loss of cortical interneuron function in schizophrenia. These include loss of a number of GABA markers in the PFC and cingulate cortex (see Lewis et al., 2005 for a review). Synaptic markers abnormally expressed in the PFC of schizophrenia patients include the vesicular glutamate transporter 1, complexin (Eastwood & Harrison, 2005), the vesicle-associated membrane protein (VAMP) (Halim et al., 2003), and BDNF (Weickert et al., 2003). The findings suggest deficits in both glutamatergic and GABAergic cortical transmission. The latter is further strengthened by observations of an abnormal population of parvalbumin-containing interneurons in the PFC of schizophrenia patients (Beasley & Reynolds, 1997). These cells express lower levels of parvalbumin and GAD67 (Hashimoto et al., 2003), probably reflecting dysfunctional interneurons and impaired inhibitory activity in these areas. There have also been reports of loss of chandelier cells, which are part of the parvalbumin-positive population (Lewis et al., 1999). PFC GABA transporter is decreased in schizophrenia (Volk et al., 2002), and there is an increase in GABA-A receptor α_2 subunits, which has been interpreted as compensation for decreased GABA innervation (Volk & Lewis, 2002). A diminished density of GABA neurons has been also reported in the cingulate cortex and hippocampus of schizophrenia patients (Benes, 1999). In addition, brains from schizophrenia patients have reduced length of TH terminals (Akil et al., 1999), indicating a decreased DA innervation, and reduced PFC spine density (Glantz & Lewis, 2000), which suggests abnormal innervation in general. These losses are not accompanied by gliosis, and therefore not the result of a degenerative process. Instead, they may have been present from earlier stages in life.

How did these early deficits fail to alter cognition or to yield symptoms before adolescence? This is a crucial question to understand the pathophysiology of schizophrenia, a disorder with clear genetic predisposition and perinatal contributing factors but yet without unequivocal symptoms until after adolescence. Imaging studies suggest abnormal post-pubertal development as an important element in schizophrenia (Pantelis et al., 2005). It can be speculated that when DA fibers establish an adult level of contact with interneurons during adolescence, they may encounter an abnormal population of GABA neurons in a brain predisposed toward schizophrenia (Benes, 1997). This may yield insufficient interneuron activation, which may not be able to filter out excessive cortical activity. Thus, the periadolescent maturation of these interneurons could be responsible for the delayed emergence of a full set of symptoms, as is proving to be the case in the NVHL model. Pre-adolescent PFC circuits are not completely normal and many behaviors served by these circuits may be affected in early stages, although to a lesser extent than the full-blown syndrome that typically emerges during the late teen years. Many studies have revealed early "prodromal" deficits in subjects that will eventually develop schizophrenia (Cannon et al., 2008). In NVHL rats, the same progression is reproduced, with some subtle anomalies present at early stages evolving into a complete set of symptoms during adolescence.

4.2. Findings in other schizophrenia models

Studies in other animal models show remarkable convergence with what has been reported in NVHL rats. Non-competing NMDA

antagonists increase glutamate levels in the PFC (Adams & Moghaddam, 1998), increase pyramidal cell firing and reduce interneuron firing (Homayoun & Moghaddam, 2007), suggesting they act via disinhibition. Elegant work by Margarita Behrens shows that ketamine affects parvalbumin interneurons via activation of inflammatory responses and induction of oxidative stress (Behrens et al., 2007; Behrens et al., 2008), offering a mechanism by which interneurons can be affected by NMDA receptor blockade. It is tempting to speculate that the effect of the NVHL procedure on PFC interneurons could be secondary to reduced NMDA activation in interneurons during development.

Other perinatal manipulations also yield reduced adult PFC parvalbumin staining. Gestational administration of the antimetabolic agent Methylazoxymethanol acetate (MAM) yields reduced PV levels in the adult PFC and hippocampus without reductions in total cell count (Lodge et al., 2009), as well as a decrease in high-frequency oscillations (Lodge et al., 2009). Attempts have been made at interfering with hippocampal activity during development without causing a lesion. Injection of the sodium channel blocker tetrodotoxin at the same time the NVHL procedure is performed, which would transiently inactivate the ventral hippocampus, also caused hyperlocomotion in adult rats (Lipska et al., 2002b). Perinatal immune challenges have been used to mimic maternal infection, and neonatal injection of the bacterial endotoxin lipopolysaccharide into the ventral hippocampus caused reduction in PV levels (Jenkins et al., 2009) and loss of the D₂ upregulation of interneuron firing in the medial PFC (Feleder et al., 2010).

Some of the genes conferring predisposition for schizophrenia have an impact on cortical interneurons. For example, NRG1 downregulates GABA-A receptors in the hippocampus, suggesting that this factor is important for the early postnatal pruning of GABA synapses (Okada & Corfas, 2004). Transgenic mice over-expressing soluble neural cell adhesion molecule (NCAM) exhibit anomalies in cortical GABA interneurons (Pillai-Nair et al., 2005). NCAM has also been found at increased levels in schizophrenia patients (Vawter et al., 2000). A truncated disrupted-in-schizophrenia 1 (DISC1) gene is present in a Scottish family with high incidence of the disease (Millar et al., 2000), and has been reproduced in a mouse in which a loss of PV activity was detected (Hikida et al., 2007). Furthermore, in utero injection of *sh*-RNA to inactivate the *DISC1* gene yields altered interneuron function in adult mice (Niwa et al., 2010). Thus, adult interneuron dysfunction seems to be a common feature of many different genetic and non-genetic manipulations.

4.3. Disinhibition: a critical feature of schizophrenia pathophysiology

All the elements reviewed above could be synthesized into a unique, yet complex, set of pathophysiological conditions. Some development- and synaptic transmission-related gene variations may predispose toward schizophrenia, most likely when combined with a perinatal environmental insult (Cannon et al., 2003). The diverse array of schizophrenia-predisposing genes would yield several windows of vulnerability during development, possibly allowing for multiple etiological factors to have a final common pathophysiology. The common results obtained using a variety of animal models highlight cortical interneurons as a possible common pathophysiological target for several different manipulations. Recent evidence indicates cytokines and inflammatory responses are activated in cortical interneurons with non-competing NMDA antagonists (Behrens et al., 2007, 2008), suggesting interneurons may be vulnerable to inflammation and oxidative stress. Imaging studies have also revealed that ketamine can increase PFC metabolic activity (Vollenweider et al., 1997). Thus, interneurons could be affected by several different factors in schizophrenia, yielding a common set of deficits by diverse etiologies that would become evident during adolescence.

NMDA receptors are critical for interneuron function. It is possible that PCP and other non-competitive NMDA antagonists could be psychotomimetic because of their blockade of NMDA receptors inside

the open channel is more effective at receptors located in interneurons. Cortical and hippocampal interneurons express NMDA receptors with NR2C and NR2D subunits, which are not detected in pyramidal neurons (Standaert et al., 1996; Scherzer et al., 1998). Different levels of NR2C and NR2D have been reported in brains from schizophrenia patients (Akbarian et al., 1996) and single-nucleotide polymorphisms in the NR2D gene have been associated with schizophrenia in a Japanese population (Makino et al., 2005). NR2D/NR1 NMDA receptors have a distinct pharmacological profile: they are less sensitive to competitive antagonists and highly sensitive to non-competing antagonists (Buller et al., 1994). They are also less sensitive to magnesium blockade (Kuner & Schoepfer, 1996), which makes them relatively easy to become activated (perhaps not needing AMPA-induced depolarization). NR2D receptors are also glycine-dependent (Williams, 1995), and this may contribute to the potential success of strategies enhancing NMDA function by blocking glycine transporter sites (Coyle & Tsai, 2004). In addition, NR2D receptors change during postnatal development. They are present in high numbers during early development and decrease later. NR2D receptors peak later than other NMDA receptor subunits during postnatal development (Monyer et al., 1994). The elevated NR2D (more “excitable”) mRNA in schizophrenia PFC may be an attempt to compensate for hypoactive interneurons. These data suggest that interneuron NMDA receptors may be a central element in schizophrenia pathophysiology.

Early neural development may be a critical period in which vulnerability for schizophrenia and related disorders may emerge. Developmental and genetic models yield altered PFC circuits in the adult animal, and loss of interneuron function is a very common observation. It is possible that schizophrenia-predisposing genes, combined with environmental factors result in altered interneuron function or connectivity via activation of inflammatory responses and oxidative stress in this discrete cell population. Animal models seem to be producing that type of outcome. In addition to proper NMDA activation in interneurons, as reviewed above, trophic factors such as BDNF could also be critical for interneuron development and their influence could be affected in the disease. So, the perinatal stage is a developmental window of vulnerability in which many different factors could alter developmental trajectories in cortical interneurons.

A second epoch of vulnerability is the period in which symptoms typically emerge: adolescence. The periadolescent period is critical for maturation of PFC circuits, and inhibitory interneurons are a central feature of such maturation (O'Donnell, 2010). If early developmental influences resulted in PFC networks with poor interneuron function, this may not yield overt behavioral deficits in the juvenile brain because interneurons are not strongly activated by DA at that time (Tseng & O'Donnell, 2007a,b). Those circuits are however vulnerable, and as they should go through the adolescent maturation, in which strong activation of interneurons by DA should be acquired, they are not able to cope with the demands imposed by that maturation. Cortical (and most importantly, prefrontal) circuits can cope with regular demands, but they may break down with increasing loads. It is possible that an improper peripubertal maturation of PFC circuitry can render the system into a state with reduced flexibility. So, conditions that normally place intense demands on re-wiring and plasticity, coupled perhaps with stress, may extenuate interneuron ability to keep pyramidal activity under control. Stress does place a high demand on DA systems, and it is conceivable that a stressful event may throw precarious PFC circuits into a largely irreversible pattern of activity. Indeed, stress is almost invariably present in the onset of schizophrenia symptoms (Thompson et al., 2004). Once pyramidal cells become exceedingly active, the system adapts, settling into a new steady state with higher basal activity and less room to further increase (which would be needed whenever working memory or response selection are required). So, although early developmental factors may have shaped a vulnerable PFC circuit and high risk for schizophrenia, periadolescent factors can exacerbate abnormal function in these circuits and yield diagnosis-level symptoms.

5. Novel therapeutic approaches

If an abnormal periadolescent maturation of cortical interneurons is critical for schizophrenia pathophysiology, agents that improve GABA function and reduce disinhibition may prove efficacious. As cortical disinhibition would yield excess glutamate release, an approach tested recently was to reduce glutamate release by activating metabotropic glutamate receptors 2/3 (mGluR2/3), which are located presynaptically and reduce glutamate release. An agent with this profile was found as effective as olanzapine in an initial clinical trial (Patil et al., 2007), and a similar drug restored behavioral performance in NVHL rats in a choice task (Gruber et al., 2010). Perhaps a better strategy in this regard would be to use positive allosteric modulators instead of direct agonists, since constant activation of mGluR2/3 could yield tolerance and unwanted effects by reducing baseline glutamate levels. A restoration of interneuron activation that should occur during DA bursts could be obtained by selectively enhancing NMDA receptors located in interneurons. In this regard, the attempts at increasing NMDA function by augmenting glycine (Coyle & Tsai, 2004) could be successful. However, if loss of interneuron function is responsible for increased pyramidal neuron excitability, a further excitation of pyramidal neurons would not be desirable. Thus, targeting NMDA receptors located in interneurons could be obtained by designing agonists that have a high affinity for NR2C or NR2D-containing NMDA receptors. Interestingly, haloperidol (the most commonly used antipsychotic) has effects on NMDA receptors fitting that profile (Ilyin et al., 1996). Since the primary drawback of this agent is the motor side-effect derived from excessive blockade of D₂ DA receptors, it would be worth searching for an agent with a similar profile on NMDA receptors and attenuated antidopaminergic activity. Alternatively (or in conjunction), the DA innervation of interneurons could be selectively targeted. Perhaps the relative efficacy of aripiprazole derives from its partial D₂ agonism (Shapiro et al., 2003). The data obtained with the NVHL model suggest that PFC interneurons do not acquire the adult modulation by D₂ receptors; however, D₁ receptors can also upregulate adult interneuron function (Tseng & O'Donnell, 2007a,b). It is conceivable that a D₁ agonist or a combination of partial D₁ or D₂ agonism with selective NMDA agonism at the NR2C or 2D subunits would offer advantages in the treatment of this devastating disorder. Because a disinhibited PFC could be directly responsible for cognitive deficits in schizophrenia, targets that restore excitation–inhibition balance can offer some hope of restoring function in the cognitive domain, which is both the one linked more strongly to quality of life in patients and resistant to current treatment strategies.

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