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Glutamatergic Synaptic Dysregulation in Schizophrenia: Therapeutic Implications

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Abstract

Schizophrenia affects approximately 1% of the population and continues to be associated with poor outcome because of the limited efficacy of and noncompliance with existing antipsychotic medications. An alternative hypothesis invoking the excitatory neurotransmitter, glutamate, arose out of clinical observations that NMDA receptor antagonists, the dissociative anesthetics like ketamine, can replicate in normal individuals the full range of symptoms of schizophrenia including psychosis, negative symptoms, and cognitive impairments. Low dose ketamine can also re-create a number of physiologic abnormalities characteristic of schizophrenia. *Postmortem* studies have revealed abnormalities in endogenous modulators of NMDA receptors in schizophrenia as well as components of a postsynaptic density where NMDA receptors are localized. Gene association studies have revealed several genes that affect NMDA receptor function whose allelic variants are associated with increased risk for schizophrenia including genes encoding D-amino acid oxidase, its modulator G72, dysbindin, and neuregulin. The parvalbumin-positive, fast-firing GABAergic interneurons that provide recurrent inhibition to cortical-limbic pyramidal neurons seem to be most sensitive to NMDA receptor hypofunction. As a consequence, disinhibition of glutamatergic efferents disrupts cortical processing, causing cognitive impairments and negative symptoms, and drives subcortical dopamine release, resulting in psychosis. Drugs designed to correct the cortical-limbic dysregulated glutamatergic neurotransmission show promise for reducing negative and cognitive symptoms of schizophrenia as well as its positive symptoms.

Keywords

Schizophrenia; NMDA receptors; Glutamate; GABA; Ketamine; D-Serine; Dopamine hypothesis; D-Amino acid oxidase; Neuregulin; Dysbindin

1 Introduction

Schizophrenia affects approximately 1% of the population and is the seventh most costly medical disorder to Society (Wu et al. 2005). With an age of symptomatic onset in late adolescence–young adulthood, the majority of patients suffer lifelong disabling symptoms

that interfere with employment and stable interpersonal relationships. The persistent disability of schizophrenia, despite over 50 years of innovation in antipsychotic drug development, suggests that the hypothesized abnormality in dopaminergic neurotransmission (Seeman 1987) does not account for the primary pathophysiology of the disorder. Indeed, three separate large-scale studies indicate that the second-generation or atypical antipsychotics, which act at dopamine receptors, are no more efficacious or tolerable than first-generation typical antipsychotics (Lieberman et al. 2005; Jones et al. 2006; Sikich et al. 2008). And both typical and atypical antipsychotics are associated with limited clinical response and poor compliance.

1.1 Dopamine Hypothesis

The dopamine hypothesis posits excessive activation of dopamine D₂ receptors as the primary pathophysiologic feature of schizophrenia (Seeman 1987). The hypothesis is based on two critical observations: (1) the clinical potency of antipsychotics in schizophrenia correlates with their affinity for the dopamine D₂ receptor, and (2) high doses of stimulants, which release brain dopamine, cause psychosis (Snyder 1981; Seeman 2002). The major limitation of the hypothesis is that typical and atypical antipsychotics, with the possible exception of clozapine, have negligible effects on cognitive impairments and negative symptoms (Meltzer 1997; Davis et al. 2003). Negative symptoms include emotional blunting, reduced motivation/drive, and asociality. Cognitive symptoms often affect executive function, attention, and working memory. It is the cognitive impairments and negative symptoms that result in persistent disability (Evans et al. 2004). Furthermore, the severity of negative symptoms and cognitive impairments correlates with the degree of cortical atrophy and ventricular enlargement (Kirkpatrick et al. 2001; Ho et al. 2003; Antonova et al. 2005; Mitelman et al. 2007; Hazlett et al. 2008), a pathologic process that proceeds for 5–10 years after onset of psychosis. Interestingly, this progressive loss of cortical volume does not appear to be due to neuronal degeneration but rather to neuronal atrophy (Pierri et al. 2001; Thune et al. 2001). Thus, a plausible theory for the pathophysiology of schizophrenia must take into account cortical atrophy and cognitive symptoms.

2 Origins of the Glutamate Hypothesis: Dissociative Anesthetics and Schizophrenia

Since dissociative anesthetics including ketamine and phencyclidine were first introduced 40 years ago, it has been appreciated that they can produce in adults a clinical picture closely resembling, if not indistinguishable, from schizophrenia, especially if they are chronically abused (Luby et al. 1959; Itil et al. 1967). Lodge and colleagues discovered that among their many other neuropharmacologic effects, the dissociative anesthetics are use-dependent, noncompetitive antagonists of the NMDA subtype of the glutamate receptor family (Anis et al. 1983). Ligand binding studies further clarified the NMDA receptor localization of the “PCP receptor” (Fagg 1987). Javitt and Zukin noted that the concentration of phencyclidine associated with psychosis was in the same range that would bind to the NMDA receptor, and proposed that schizophrenia might result from hypofunction of NMDA receptors (Javitt and Zukin 1991). However, there were concerns with this causal interpretation, an alternative

explanation being that individuals who abused PCP or ketamine might be at high risk for a schizophrenic-type reaction (Bowers and Swigar 1983).

2.1 Ketamine Challenge

In a landmark study, Krystal et al. (1994) directly addressed this concern by demonstrating that infusion of low, sub-hypnotic doses of ketamine into normal volunteers in a laboratory setting produced negative symptoms including blunted affect and withdrawal and rather selective impairments in memory and cognition that are specifically associated with schizophrenia. Acute administration of ketamine in normal subjects did not produce a robust re-creation of positive symptoms such as hallucinations, although paranoia, thought disorder, and loose associations were evident. Nevertheless, patients with schizophrenia who were not receiving antipsychotics exhibited a significant exacerbation of positive symptoms that were unique to the given patient after administration of low dose ketamine (Lahti et al. 2001). The remarkable similarities in the subtle cognitive abnormalities observed in schizophrenia and the effects of low dose ketamine in normal volunteers were elaborated upon by others (Adler et al. 1999; Newcomer et al. 1999).

Subsequent studies using the low dose ketamine paradigm in normal subjects demonstrated that it also produced physiologic abnormalities associated with schizophrenia. These abnormalities, which are not considered in the clinical diagnosis of schizophrenia, are nonetheless reflective of the underlying pathology of the disease, and are therefore called “endophenotypes.” Smooth pursuit and anti-saccade eye tracking abnormalities are an endophenotype of schizophrenia (Holzman et al. 1988). Low dose ketamine disrupts eye tracking in normal individuals (Radant et al. 1998). PET imaging studies that monitor the displacement of [^{11}C]raclopride by endogenous dopamine demonstrated increased dopamine release in the striatum with an amphetamine challenge in schizophrenia patients as compared to controls (Kegeles et al. 2000). Pretreatment with a low dose ketamine caused healthy control subjects to also exhibit increased dopamine release with amphetamine challenge as compared to placebo-treated controls. Sensory gating abnormalities are common in schizophrenia and reflect abnormal cortical and subcortical information processing.

Such abnormalities can be studied noninvasively in a laboratory setting in humans as well as animals. For example, prepulse inhibition (PPI) of the acoustic startle response is observed when the response to a startling stimulus is reduced when preceded by a few milliseconds by a non-startling tone. Individuals with schizophrenia exhibit impaired PPI (Braff et al. 1978). Treatment of experimental animals such as rodents with ketamine causes disruption in PPI in an analogous fashion to what is observed in schizophrenia (Geyer et al. 2001). Surprisingly, normal human adults exhibit enhanced PPI when given an acute ketamine challenge (Braff et al. 2001). While this discrepancy might suggest that PPI deficits in schizophrenics are not due to NMDA receptor hypofunction, recent research indicates that acute ketamine challenge results in a rebound increase in glutamatergic neurotransmission (Li et al. 2010). Individuals with schizophrenia exhibit behavioral evidence of temporal information processing deficits and reduced mismatch negativity (MMN) in sensory event-related brain

potentials (Javitt et al. 1993), which can be produced in healthy control subjects by low dose ketamine (Umbricht et al. 2000).

3 Neurochemistry of the Glutamatergic Synapse in Schizophrenia

Many features of the pathophysiology of schizophrenia implicate neuroanatomic, organizational, and functional features of the corticolimbic glutamatergic system. Glutamatergic pyramidal cells are the projecting neurons that interconnect prefrontal cortex, temporal cortex/hippocampus, and thalamus, regions of the brain which structural and functional brain imaging studies have demonstrated to exhibit abnormalities in schizophrenia (Hulshoff and Kahn 2008). Furthermore, the NMDA subtype of glutamate receptor plays multiple roles in brain functions that have been implicated in the cellular pathology of schizophrenia. These include regulating neuronal migration (Komuro and Rakic 1993), neuronal differentiation (Pearce et al. 1987), response to trophic factors (Black 1999), functional plasticity such as long-term potentiation (LTP) (Harris et al. 1984) of synaptic transmission, and the development of dendritic spines (Yasumatsu et al. 2008). Abnormal migration of cortical GABAergic interneurons (Akbarian et al. 1993), neuronal atrophy (Sweet et al. 2004), and reduced dendritic spines (Sweet et al. 2009) have all been observed in schizophrenia.

3.1 NMDA Receptor Modulators

Postmortem studies have provided convincing evidence that disruption in the modulation of NMDA receptors is part of the pathophysiology of schizophrenia. In addition to the glutamate recognition site on NR2 subunit, the NR1 subunit has a binding site for glycine and D-serine (also known as the *glycine B receptor* to distinguish it from the inhibitory glycine receptor) (Kuryatov et al. 1994) that must be occupied in order for glutamate to open the ion channel (Johnson and Ascher 1987; Kleckner and Dingledine 1988). D-Serine is a full agonist at the glycine B receptor on the NMDA receptor (Matsui et al. 1995). Tissue levels of D-serine are determined by the activity of its synthetic enzyme, serine racemase, and the activity of its catabolic enzyme D-amino acid oxidase (Schell et al. 1995; Wolosker et al. 1999a, b). Notably, serine racemase expression is high in the corticolimbic regions of the brain whereas D-amino acid oxidase expression is quite low in these regions (Hashimoto et al. 1993; Schell et al. 1995). *Postmortem* studies have demonstrated increased D-amino acid oxidase activity and transcript levels in subregions of the cerebral cortex in subjects with a diagnosis of schizophrenia as compared to controls or those with a diagnosis of bipolar disorder (Kapoor et al. 2006; Madeira et al. 2008; Burnet et al. 2008). The increases in D-amino acid oxidase in schizophrenia vary from approximately 30% to twofold and are unrelated to neuroleptic exposure. In contrast, serine racemase activity and mRNA are relatively unaffected in schizophrenia. Measurement of the cerebral spinal fluid (CSF) of living subjects with schizophrenia has revealed reduced levels of D-serine, although *postmortem* brain tissue levels do not appear abnormal (Hashimoto et al. 2005; Bendikov et al. 2006). However, *postmortem* tissue levels of D-serine may imperfectly reflect its functional status since the regulation of its synthesis is dynamic and influenced by presynaptic glutamatergic neuronal activity (Kim et al. 2005).

Glutamate carboxypeptidase II (CGPII) hydrolyzes the neuropeptide *N*-acetyl-aspartyl glutamate (NAAG) (Robinson et al. 1987), which is co-localized with and released by corticolimbic glutamatergic pyramidal neurons (Passani et al. 1997; Bergeron et al. 2005) as well as components of other neuronal systems (noradrenergic locus coeruleus neurons, cholinergic motor neurons, limbic GABAergic neurons) (Berger et al. 1999). NAAG selectively inhibits NMDA receptor currents in a glycine-reversible fashion (Bergeron et al. 2005). It also is an agonist at mGluR3 receptors that downregulate glutamate release (Bischofberger and Schild 1996; Wroblewska et al. 1997), although recent findings in the mouse perforant pathway contradict these conclusions (Fricker et al. 2009). Five *postmortem* studies carried out with different patient cohorts have demonstrated reduced enzymatic activity, protein levels, and mRNA for GCPII in corticolimbic structures in schizophrenia (Tsai et al. 1995; Hakak et al. 2001; Tkachev et al. 2007; Guilarte et al. 2008; Ghose et al. 2004, 2009).

Kynurenic acid is a metabolite of tryptophan that inhibits NMDA receptors by blocking the glycine B receptor site (Birch et al. 1988; Mayer et al. 1988). It is also an antagonist of the alpha 7-nicotinic receptor (Hilmas et al. 2001), which has also been implicated in schizophrenia (Martin and Freedman 2007). Systemic treatment of rats with kynurenic acid, like dissociative anesthetics, causes dopaminergic neurons in the ventral tegmental area (VTA) to exhibit burst firing, which can be reversed by treatment with the partial glycine B receptor agonist, D-cycloserine (DCS) (Erhardt and Engberg 2002). A *postmortem* study revealed elevated kynurenic acid levels in the prefrontal cortex of schizophrenics as compared to controls (Schwarcz et al. 2001). Several studies of CSF have shown elevated levels of kynurenic acid in schizophrenia (Erhardt et al. 2001, 2003; Nilsson et al. 2005). Kynurenine 3-monooxygenase, an enzyme critical for kynurenic acid disposition, is downregulated in the cortex in schizophrenia, and its gene is associated with increased risk for the disorder (Wonodi et al. 2011). Preclinical studies involving both pharmacologic manipulations as well mouse mutants demonstrate that modest changes in endogenous levels of kynurenic acid unequivocally alter NMDA receptor function (Coyle 2006).

3.2 Postsynaptic Density in Schizophrenia

NMDA receptors are anchored in the postsynaptic density (PSD), a protein complex with which over a 100 other proteins are associated (Dosemeci et al. 2007). Postmortem studies have measured subunits of the NMDA receptors as well as components of the PSD. Meador-Woodruff and colleagues described reductions in NMDA, AMPA, and kainate receptor subunits in the thalamus (Ibrahim et al. 2000) as well as PSD-95, SAP102, and NF-L; PSD-95 and NF-L were reduced in the anterior cingulate cortex (Kristiansen and Meador-Woodruff 2005; Kristiansen et al. 2006), the latter which is also affected in bipolar disorder. Decreases in NR2B and PSD-95 in the endoplasmic reticulum in the prefrontal cortex in schizophrenic subjects suggest altered processing (Kristiansen et al. 2010). Toyooka et al. similarly found significant reductions in the expression of SAP 97 in prefrontal cortex and SAP102 in hippocampus and in the prefrontal cortex in schizophrenia (Ohnuma et al. 2000; Toyooka et al. 2002). The most consistent changes involved NF-L, SAP102, PSD-95, and PSD-93, which were reported to be reduced in the anterior cingulate cortex and the dorsolateral prefrontal cortex (DLPFC). An increased transcript expression was associated

with decreased protein expression of PSD-95. Other synaptic components involved in glutamatergic neurotransmission are also affected in schizophrenia. The excitatory amino acid transporters (EAAT1 and 2) are elevated in the thalamus (Huerta et al. 2006), which should further compromise glutamatergic neurotransmission. Consistent reductions in the kainic acid receptor have been described using ligand binding (Scarr et al. 2005) and in situ hybridization or RT-PCR of mRNA encoding its subunits (Porter et al. 1997; Beneyto et al. 2007) in studies of prefrontal cortex and hippocampus in schizophrenia (Sokolov 1998; Wilson et al. 2006). Furthermore, immunohistochemical studies revealed significant reductions in the density of GluR5, 6, 7 immunoreactivity on the pyramidal cell dendrites found in both the *stratum radiatum* as well as the *stratum moleculare* of hippocampal sectors CA1, 2, and 3 in patients with schizophrenia (Benes et al. 2001). In the anterior cingulate cortex, the density of GluR5 expressing interneurons was reduced by ~40% in schizophrenia and in bipolar disorder (Woo et al. 2007). These findings are consistent with the results of case-control and association studies that implicate genes encoding the kainic acid receptor subunits and risk for schizophrenia (Pickard et al. 2006; Begni et al. 2002).

4 Are There Sensitive Developmental Periods for NMDAR Hypofunction in Schizophrenia Risk?

The ~50% concordance rate for schizophrenia in monozygotic twins indicates that the disease is both genetic and environmental in etiology (Cardno and Gottesman 2000). It is therefore important to consider environmental factors and their biological substrates. In contrast to the modest amount of risk conferred by any individual putative schizophrenia gene identified to date, environmental events such as prenatal influenza infection and severe maternal stress increase schizophrenia risk ~3–5-fold (Tandon et al. 2008). These strong epidemiological findings point to a sensitive period in brain development during which the fetus may be more vulnerable to accumulating insults that predispose the individual to schizophrenia in adulthood. Though the specific biological mechanisms of these insults have not yet been elucidated, the multiple roles of NMDAR-mediated neurotransmission in brain development of preclinical species are widely documented (Shatz 1990; Scheetz and Constantine-Paton 1994; Penn 2001).

4.1 Perinatal NMDA Receptor Antagonist Models

Application of NMDAR antagonists during early postnatal development results in many phenomena related to the schizophrenia endophenotype in adulthood. Based on detailed modeling of the timing of key neurodevelopmental events, the first two postnatal weeks in the rat are considered roughly equivalent to human fetal development at the second trimester of pregnancy (Clancy et al. 2001). Perinatal blockade of NMDARs with PCP or MK-801 within this time frame has been shown to cause deficits in PPI of the acoustic startle reflex in adult rats (Harris et al. 2003; Takahashi et al. 2006). Elevated PCP- and amphetamine-induced hyperlocomotion have been observed during adolescence and adulthood in rats treated perinatally with PCP, indicating dysregulation of glutamatergic and dopaminergic neurotransmission, respectively (Wang et al. 2001; Depoortère et al. 2005). Early postnatal MK-801 treatment results in persistent cognitive deficits in set-shifting and working memory (Stefani and Moghaddam 2005). Treatment with PCP during this period has resulted in

deficits in spatial reference, reversal, and spatial working memory, during adolescence and adulthood (Sircar 2003; Andersen and Puzet 2004). Encouraging for the prospects of novel therapeutics, some adult deficits have been attenuated by treatment with D-serine or a selective inhibitor of glycine transporter-1, both of which result in increased NMDAR-mediated neurotransmission (Depoortère et al. 2005; Andersen and Puzet 2004).

Early postnatal NMDAR blockade also recapitulates a pathological hallmark of schizophrenia, a decrease in parvalbumin (PV)-positive interneurons in hippocampus and cortex (Beasley et al. 2002; Zhang and Reynolds 2002; Knable et al. 2004; Reynolds et al. 2004). Transient postnatal administration of PCP resulted in a selective decrease in PV-positive neurons in adult primary somatosensory, motor, and retrosplenial cortices (Wang et al. 2008). Prenatal administration of MK-801 resulted in a selective decrease in PV-positive neurons in adult medial prefrontal cortex (Abekawa et al. 2007). Although selective reduction in PV can be achieved by subacute administration of NMDAR blockers in adult rodents (Zhang et al. 2008), the findings that this neuropathology can be induced by perinatal administration and be evident several weeks later in the mature brain demonstrate that the developing brain is vulnerable to NMDAR hypofunction and that this type of manipulation leaves a lasting lesion.

4.2 Adolescence and NMDA Receptors

If the perinatal period is the first environmental “risk window” for schizophrenia, late adolescence/early adulthood is the next phase of the disease in which neurodevelopmental events are of acute interest, as this is the period during which psychotic symptoms typically emerge. Onset of schizophrenia corresponds to the timing of significant pruning of cortical synapses that are located on dendritic spines (Bourgeois et al. 1994). *Postmortem* studies have shown that the density of these spines on layer III frontal and temporal cortical pyramidal neurons is significantly reduced in schizophrenia (Lewis 1997; Garey et al. 1998; Glantz and Lewis 2000). The pruning process is regulated by neuronal activity (Segal and Andersen 2000), and one can hypothesize multiple ways in which the pathological and genetic findings related to NMDA-mediated neurotransmission might contribute to dysregulation at this stage. For example, the depressed NR1 expression and elevated NR2B expression observed in schizophrenia (Gao et al. 2000) may interfere with the pruning process in a variety of ways, by resulting in hypofunction of NMDAR-mediated neurotransmission, or excitotoxicity or the potentiation of inappropriate synapses due to increased Ca^{2+} influx through NMDARs.

4.3 Myelination

Another major process of brain development peaking during late adolescence/early adulthood is the myelination of the brain, which supports the connectivity between different brain areas implicated in schizophrenia pathology (Benes 1989). Diffusion tensor imaging of white matter has revealed white matter abnormalities in schizophrenia, although it is difficult to distinguish between loss of coherence of white matter tracts, loss of fibers, and loss of myelination using these methods (Kubicki et al. 2005, 2007). Results of functional imaging studies have suggested that there is disruption of the temporal synchrony of functional neural networks in the brain in schizophrenia (Ragland et al. 2007). The oligodendroglial processes

that extend to myelinate axons express NMDA receptors during development (Salter and Fern 2005). The recent finding that prenatal PCP exposure retards oligodendrocyte maturation, resulting in fewer myelin-producing cells, provides a direct link between NMDAR-mediated neurotransmission, early development, and myelination (Lindahl et al. 2008).

5 Schizophrenia Risk Genes and Glutamatergic Neurotransmission

Currently, there is debate over the reliability of findings for risk genes identified in association studies. Some have argued that genetic evidence, unbiased with respect to candidate-gene-based hypotheses, suggests that copy number variants (CNVs) involving deletions or reduplications of stretches of DNA or new mutations account for up to 10% of genetic risk (International Schizophrenia Consortium 2008). Nevertheless, meta-analyses of the results of whole genome-wide association studies (GWAS) do point to several genes that plausibly confer risk for schizophrenia (Allen et al. 2008; Shi et al. 2008b). The underlying assumption is that schizophrenia is a disorder of complex genetics in which multiple risk alleles of moderate effect interact with environment to produce the phenotype. SZGene (<http://www.szgene.org>) provides a frequently updated comprehensive, unbiased meta-analytic compendium of the results of association studies in schizophrenia that rates the strength of the association.

5.1 D-Amino Acid Oxidase

One of the first putative risk genes to emerge from an expanded association study involving 191 SNPs over a 5-Mb region of 13q34 was G72 (Chumakov et al. 2002). It encodes for a protein that binds to D-amino acid oxidase (DAAO), the enzyme that catabolizes D-serine and plays an important role in regulating its tissue levels. It is of relatively recent evolutionary appearance, being present only in primates. Originally, it was thought that G72 activated DAAO, thus its designation DAO *activator* (DAOA). However, more recent research has shown that cultured cells, which have been transfected with G72, generate a protein that inhibits DAAO (Sacchi et al. 2008). Thus, mutations in G72 (SZGene rank #12) would likely result in disinhibition of DAAO, thereby reducing the availability of D-serine. Since G72 was first proposed as a risk gene for schizophrenia, over a dozen studies have supported this association (Shi et al. 2008a). The impressively replicable association of G72 with the risk for schizophrenia converges with clinical findings that serum and CSF D-serine levels are reduced in subjects with schizophrenia (Hashimoto et al. 2003, 2005). Furthermore, placebo-controlled clinical trials have demonstrated that D-serine reduces negative symptoms, improves cognition, and reduces positive symptoms in patients with chronic schizophrenia who are receiving concurrent typical antipsychotic medications (Tsai et al. 1998; Heresco-Levy et al. 2005).

Several association studies have shown that the gene encoding DAAO (SZGene #40) itself is also linked to the risk of schizophrenia (Chumakov et al. 2002; Schumacher et al. 2004; Liu et al. 2004). Although the enzymatic consequences of DAAO allelic variation are not known, the fact that *postmortem* studies reveal elevated activity and expression levels of DAAO in the hippocampus and forebrain of patients with schizophrenia suggests that variants associated with the disorder should alter DAAO in this direction (Kapoor et al. 2006;

Madeira et al. 2008). Notably, one study found a robust epistatic interaction between the DAAO gene and the DAOA gene in schizophrenia with an odds ratio of 9.3 (Corvin et al. 2007). A less robust but replicated finding suggests that serine racemase (SZGene rank #45) itself may be a risk gene for schizophrenia (Morita et al. 2007). A single nucleotide polymorphism in the 5' promoter region of the gene is associated with schizophrenia and results in reduced expression of serine racemase (Goltsov et al. 2006). This would result in reduced D-serine levels and consequent NMDAR hypofunction. PICK 1, a protein that interacts with serine racemase (Fujii et al. 2006), has also been identified as a possible risk gene for schizophrenia in a Han Chinese population (Hong et al. 2004). A recent meta-analytic study has implicated the gene encoding the NMDA receptor subunit NR2B (GRIN2B: SZGene rank #39) in schizophrenia risk (Li and He 2007). This subunit is associated with greater conductance of Ca^{2+} than the other NR2 subunit isoforms, is highly expressed during development, and normally drops off in expression in adulthood (Hall et al. 2007).

5.2 Dysbindin

Dysbindin (DNTBP1; 6p24; SZGene rank #20) is another promising risk gene for schizophrenia, in that its association with schizophrenia has been replicated in several independent studies and it has strong biological plausibility (for review, see Williams et al. 2005). The dysbindin protein is concentrated in the presynaptic glutamatergic terminals where it interacts with synapsin 1 and SNAP, modulating the vesicular release of glutamate (Numakawa et al. 2004). The expression of dysbindin is reduced in the prefrontal cortex and hippocampus in schizophrenia (Talbot et al. 2004; Weickert et al. 2004). Consistent with the profile of a risk gene, the dysbindin genotype associates inversely with general cognitive ability and poor premorbid function in schizophrenia (Burdick et al. 2006; Gornick et al. 2005).

5.3 Neuregulin

The association of the gene encoding neuregulin (SZGene rank #26) with the risk for schizophrenia is quite robust (Petryshen et al. 2005). Neuregulin (NRG) is a member of the ErbB signaling pathway that regulates neuronal development, migration, myelination, and synaptic maintenance (for review, see Mei and Xiong 2008). A neuregulin 1 hypomorph mouse displays abnormal behaviors that are reversed by the atypical antipsychotic clozapine and exhibits reduced phosphorylation of the NR2B subunit at Y1472, resulting in NMDA receptor hypofunction (Bjarnadottir et al. 2007). A hypomorph of the type 3 NRG1 isoform has enlarged lateral ventricles, decreased spine density, hypofunction of the prefrontal cortex and hippocampus, and deficits in prepulse inhibition (Chen et al. 2008). Thus, both mouse models share important endophenotypic features with schizophrenia. Using a postmortem tissue stimulation approach, Hahn et al. (2006) showed a marked increase in NRG1-induced activation of ErbB4 in the prefrontal cortex in schizophrenia, although the absolute levels of NRG1 ErbB4 did not differ significantly between schizophrenia and control groups.

6 Corticolimbic GABAergic Deficits in Schizophrenia

Thirty years ago, Spokes et al. (1980) first reported reduced activity of glutamic acid decarboxylase (GAD) in cortex and GABA in the nucleus accumbens and thalamus in a postmortem study in patients with schizophrenia as compared to suitable controls. However, the findings were highly variable, and other studies suggested that the loss of GAD activity may be an artifact of a slow death, to which institutionalized schizophrenic patients were particularly prone (Perry et al. 1982; Spokes 1979). Recent studies from several laboratories utilizing brain bank tissue from diverse sources have described compelling reductions of the presynaptic markers for a subpopulation of GABAergic interneurons in the frontal cortex and in the hippocampal formation (for review, see Akbarian and Huang 2006). Two genetically distinct forms of glutamic acid decarboxylase (GAD) have been identified on the basis of molecular weight (65 and 67 kDa) (Bu et al. 1992). GAD67 is preferentially expressed in perikarya and dendrites, whereas GAD65 is more prominently expressed in axons and terminals (Kaufman et al. 1991). Several studies have described reduced numbers of GAD67 mRNA expressing neurons in the prefrontal cortex and an overall reduced expression of GAD67 as compared to GAD65 (Akbarian et al. 1995; Volk et al. 2000; Heckers et al. 2002; Woo et al. 2004). In a laminar analysis, Volk et al. (2001) reported that the density of neurons with detectable GAD67 mRNA was significantly decreased in the intermediate layers of the prefrontal cortex, but that the level of GAD67 mRNA expression per neuron did not differ from control subjects.

6.1 Parvalbumin-Positive GABAergic Neurons

GABAergic interneurons also express calcium binding proteins including calretinin, calbindin, and parvalbumin (Conde et al. 1994). The levels of expression of these proteins are modulated by afferent synaptic activity (Philpot et al. 1997). Parvalbumin is expressed predominantly in chandelier and basket cells in the cortex, which receive direct input from pyramidal neurons. Their synaptic contacts are concentrated on the proximal axon in structures known as “cartridges” and the soma of the pyramidal cell, thereby exerting a major influence over pyramidal cell firing. These are fast-firing interneurons that coordinate cortical excitatory output. Calbindin is localized to double bouquet cells; calretinin is found in both double bouquet and bipolar neurons. The expression of parvalbumin, but not calretinin, was reduced in the prefrontal cortex in schizophrenia (Beasley and Reynolds 1997). In contrast to GAD67, which was associated with a significant reduction of positive neurons, the number of neurons with parvalbumin mRNA in the prefrontal cortex was unchanged in patients with schizophrenia, whereas the amount of mRNA per neuron was significantly decreased (Hashimoto et al. 2003). Reduced expression of GAD67 and parvalbumin in the prefrontal cortex has been replicated in studies using DNA chip array (Mirnics et al. 2006). Furthermore, real-time quantitative PCR of the prefrontal cortex, anterior cingulate cortex, the primary motor cortex, and primary visual cortex has shown that there were comparable reductions in the mRNA encoding for somatostatin, PV, GAD67, the GABA membrane transporter, GAT-1, and the $\alpha 1$ and δ subunits of the GABA-A receptors (Lewis and Hashimoto 2007). In contrast, the expression of calretinin mRNA did not differ between schizophrenia patients and matched controls (Hashimoto et al. 2008).

GAT1 is another specific presynaptic marker for GABAergic neurons. Initial studies describe significant reductions in GAT1 expression in the prefrontal cortex and hippocampus in schizophrenia as determined by ligand binding methods (Reynolds et al. 1990; Schleimer et al. 2004). Using in situ hybridization, Volk et al. (2001) reported that GAT1 expression was decreased below the level of detectability in a subpopulation of GABAergic interneurons in the intermediate layers of the dorsolateral prefrontal cortex. GAT1 immunocytochemistry revealed a reduced density of the cartridges of GABAergic terminal boutons innervating the pyramidal cell proximal axons (Woo et al. 1998).

6.2 Reduced GABAergic Tone?

Reduction in GAT1 would lead to enhanced GABAergic neurotransmission, whereas a reduction in GAD67 might be associated with reduced GABAergic neurotransmission. Studies of GABA-A receptors support the latter scenario of persistent decreased GABAergic neurotransmission at these synapses. Early studies using ligand binding techniques revealed a 40% increase $B_{\max}$ but no change in the KD for the specific binding of [3H]GABA (Benes et al. 1996). Later studies demonstrated significant increases in [3H]muscimol binding to GABA_A receptors in subfields of the hippocampal formation, the anterior cingulate cortex, and the prefrontal cortex (Hanada et al. 1987). With high resolution, the increase in GABA_A receptors could be localized to pyramidal neurons in the intermediate layers of the cortex (Benes et al. 1992). Volk et al. (2002) reported a doubling of the GABA_A $\alpha 2$ -immunoreactive axon initial segments of the pyramidal neurons where the GABAergic chandelier cell cartridges are concentrated. Alpha 1 and $\alpha 5$ subunits of the GABA-A receptor were also reportedly increased in the prefrontal cortex by Impagnatiello et al. (1998).

7 Which NMDA Receptors Are Hypofunctional?

NMDA receptors are ubiquitous in the brain and peripheral nervous system. The studies in which low dose ketamine was used to induce symptomatic features of schizophrenia in normal individuals, given their normal performance on the Mini Mental Status Exam, suggest that a very discrete subpopulation of NMDA receptors were being affected under these experimental conditions. The first hint of differential sensitivity of neurons to NMDA receptor antagonists may have been the study by Grunze et al. (1996), which reported that GABAergic interneurons in the CA1 region of the hippocampus were tenfold more sensitive to the canonical NMDA receptor antagonist, amino-phosphono-valeric acid (APV), and to NAAG than those on the pyramidal neurons receiving the same Schaffer collateral input. In rodents, the pyramidal neurons in the limbic cortex, especially the retrosplenial cortex, are vulnerable to the excitotoxic effects of dissociative anesthetics with dramatic overexpression of heat shock proteins (Sharp et al. 1991). These cyto-pathologic effects were attenuated by muscimol, a GABA-A receptor agonist (Sharp et al. 1994). On examining the electrophysiologic mechanisms responsible for these neuropathologic changes induced by dissociative anesthetics, Li et al. (2002) found that in acute slice preparations from the rat limbic cortex, the NMDA receptors on the GABAergic interneurons were disproportionately more sensitive to the antagonist effects of MK-801 as compared to NMDA receptors on pyramidal neurons. Homayoun and Moghaddam (2007) reported that NMDA receptor

inhibition in acute prefrontal slices from rat caused a reduction in GABAergic interneuron firing and a delayed disinhibition of the pyramidal neurons. Research by Jodo et al. (2005) demonstrates that increased firing of prefrontal pyramidal neurons can be produced by local infusion of MK-801 in the ventral hippocampus.

7.1 NMDA Receptor Antagonists and Parvalbumin-Positive GABAergic Neurons

Several studies now demonstrate that subacute or chronic treatment with dissociative anesthetics including PCP, ketamine, and MK-801 produces a downregulation of presynaptic GABAergic markers including GAD67, PV, and GAT1 in the frontal cortex of rats and mice. Pratt and colleagues have also demonstrated reduced expression of Kv3.1, hypofrontality as demonstrated by 2-deoxyglucose autoradiography, and impairments in executive functions (for review, see Pratt et al. 2008). Kinney found that the changes in parvalbumin and GAD67 immunoreactivity were reversible and were fully replicated with an NR2A-selective antagonist but only partially by an NR2B-selective antagonist (Kinney et al. 2006). Behrenset al. (2007) further demonstrated that NMDA receptor blockers produce a burst of superoxide due to activation in neurons of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Pharmacologic treatments that decrease superoxide production prevent the effects of ketamine on inhibitory interneurons of the prefrontal cortex. An electrophysiologic analysis of acute frontal cortical slices prepared from mice treated subchronically with ketamine indicated that the frequency and magnitude of inhibitory postsynaptic potentials (IPSPs) were significantly reduced on pyramidal neurons, and the excitability of the pyramidal neurons was significantly increased (Zhang et al. 2008).

7.2 A Pathologic Circuit?

Lisman et al. (2008) put forward a hypothesis that the counterintuitive disinhibition of the glutamatergic pyramidal neurons after treatment with an NMDA receptor antagonist reflected the substantial contribution (~30%) of NMDA receptor channels to the excitatory postsynaptic currents (EPSCs) on GABAergic interneurons so that reduced NMDA receptor channel activity would have substantial impact on interneuron excitability. Intracellular Ca^{2+} levels could serve as a proxy for GABAergic neuronal firing. AMPA receptors, unlike NMDA receptors, generally do not conduct Ca^{2+} . Thus, in spite of increased glutamatergic input to these fast-firing GABAergic interneurons, they “misperceive” reduced glutamatergic neurotransmission because the decreased NMDA receptor function caused by exogenous dissociative anesthetics or by endogenous inhibitors, such as kynurenic acid and NAAG, restricts Ca^{2+} influx. To correct for this “misperceived” reduced excitatory input, the PV-positive GABAergic interneurons decrease the expression GAD67 and release of GABA as well as the Ca^{2+} buffering protein, parvalbumin (Lisman et al. 2008).

7.3 Psychosis as a Downstream Event

While the appearance of psychosis heralds the onset of schizophrenia, psychosis is not unique to schizophrenia and occurs in bipolar disorder, major depressive disorder, and Alzheimer’s dementia. The central role of excessive stimulation of dopamine D_2 receptors in the pathology of psychosis is well established as essentially all antipsychotic drugs act via blocking dopamine D_2 receptors. While dysfunction of the dopamine system must be accounted for in any hypothesis about the etiology of schizophrenia, a primary deficit in

dopaminergic neurotransmission does not explain many aspects of the schizophrenia prodrome, endophenotypes, and clinical course under treatment with currently available antipsychotics.

NMDA receptor antagonists have been shown to produce a hyperdopaminergic state in both experimental animals as well as humans (Moghaddam and Adams 1998; Kegeles et al. 2000). While the disinhibition of glutamatergic outputs appears to be widespread in the corticolimbic system, disinhibition of the glutamatergic output from the subiculum to the VTA appears to be critical for producing the hyperdopaminergic state with systemic treatment with dissociative anesthetics (Lisman et al. 2008). Thus, psychosis would be considered a “downstream” event. This interpretation of the pathophysiology of psychosis in schizophrenia has now received compelling support from a recent clinical trial that demonstrated that an mGluR2/3 agonist, which downregulates disinhibited glutamate release, exhibits antipsychotic effects roughly comparable to the atypical antipsychotic, olanzapine (Patil et al. 2007). Preclinical studies demonstrated that activation of the mGluR2/3 receptor downregulated the excessive dopamine release caused by treatment with NMDA receptor antagonists (Fell et al. 2008).

8 Conclusion

While the role of dopamine in the pathophysiology of psychosis is secure, the inadequacy of antipsychotic medications to address the cognitive deficits and negative symptoms of schizophrenia suggest that dopamine D₂ receptor antagonism is not addressing the core pathophysiology of schizophrenia. Viewed from a circuit perspective, one can now appreciate that each of these neurotransmitters plays a distinct, contributory role to the overall phenotype of schizophrenia (Fig. 1). We propose that the NMDA receptors on the fast-firing, PV-positive cortical GABAergic interneurons are hypofunctional secondary to elevated endogenous inhibitors, deficient co-agonists, NR2B mutations, or negative modulation. This neuron-selective NMDA receptor hypofunction results in reduced inhibitory feedback to pyramidal cells, causing increased excitatory output and disruption of the integrity of cortical columnar processing (Coyle et al. 2010). In addition, hypo-function of NMDA receptors on the pyramidal neurons themselves may account for their smaller size, reduced dendritic complexity, and reduced number of spines (Balu et al. 2012). These primary functional abnormalities in the cortex (disinhibition and atrophy) would account for cognitive impairments and negative symptoms as supported by computational modeling (Grunze et al. 1996; Vierling-Claassen et al. 2008; Lisman et al. 2008). Consistent with this interpretation, default functional brain imaging in schizophrenia reveals hyperactivation and reduced task-related suppression in default regions in schizophrenia (Whitfield-Gabrieli et al. 2009). Disinhibition of the excitatory output of the *subiculum* would drive increased dopaminergic VTA neuronal activity and secondary psychosis.

Thus, the dysregulation of glutamatergic neurotransmission depends upon which neuronal components of the circuit are considered. Evidence supports hypofunction of NMDA receptors on cortical GABAergic and pyramidal neurons but excess glutamate release from the glutamatergic cortical efferents. Understanding of the pathologic circuitry yields a much wider array of drug targets that might effectively address the cognitive impairments and

negative symptoms neglected by current dopamine D₂ receptor blockers. For example, plausible targets would include agents that enhance NMDA receptor function such as GlyT1 inhibitors (Bergeron et al. 1998), glycine B receptor agonists (Goff et al. 1995; Tsai and Lin 2010), mGluR5 agonists (Conn et al. 2009), drugs that enhance GABA_A receptor function (Lewis et al. 2008), or drugs that attenuate glutamate release such as mGluR2/3 agonists or positive modulators (Patil et al. 2007).

Such novel interventions would presumably have acute/subacute effects on symptoms including cognition, negative symptoms, and conceivably psychosis. However interventions that enhance NMDA receptor function or downstream intracellular mediators of NMDA receptor function could also conceivably foster neural plasticity and even increased neural connectivity, given the evidence that D-cycloserine enhances memory consolidation in both experimental animals and human subjects receiving cognitive behavioral therapy for anxiety disorders (Davis et al. 2006), it will be important to determine whether coupling NMDA receptor potentiators with cognitive rehabilitation significantly improves outcome. Given the circumstantial evidence that in addition to its many other actions clozapine enhances NMDA receptor function (Coyle et al. 2002), one can draw hope from its effects in treatment-refractory schizophrenia (Kane 1992) that NMDA receptor directed treatments might provide additional benefit. Finally, the variety of targets available in this pathologic circuitry may dovetail with the emergence of personalized medicine as the complex genetics of schizophrenia and related serious psychiatric disorders are illuminated.

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Fig. 1.

Schematic representation of the critical circuitry involved in the pathophysiology of schizophrenia. NMDA receptor (NMDAR) hypofunction can result from multiple causes including exogenous antagonists such as ketamine, endogenous antagonists such as *N*-acetylaspartyl-glutamate (NAAG) or kynurenic acid or products of risk genes D-amino acid oxidase activator (*DAOA*), dysbindin (*DTNBP1*), neuregulin 1 (*NRG1*), kainite receptor 3 (*GRIK3*), NR2B (*GRIN2B*), D-amino acid oxidase (*DAO*) and serine racemase (*SR*). NMDAR hypofunction on cortico-limbic pyramidal cells cause atrophy with reduced dendritic complexity, reduced spine density and reduced connectivity. NMDAR hypoactivity on the fast-firing, parvalbumin-positive cortical GABAergic neurons results in disinhibition of pyramidal cell efferents, causing cognitive impairments and excessive drive of ventral tegmental area (VTA) dopaminergic neurons resulting in psychosis. (Adapted from Coyle et al. 2010)