Chapter

DOPAMINERGIC AND GLUTAMATERGIC DYSFUNCTIONS IN THE NEUROPATHOPHYSIOLOGY OF SCHIZOPHRENIA

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ABSTRACT

Schizophrenia is a devastating mental disorder that affects almost 1% of the human population. Although the etiology and fundamental pathological processes associated with schizophrenia remain unclear, abnormalities of the dopamine and glutamate systems have been implicated in their occurrence. The putative role of dopamine in the pathophysiology and treatment of schizophrenia has been studied intensively in past decades. The central importance of dopaminergic dysfunctions is clearly evidenced by the efficacy of dopamine D_2 receptor antagonists in the treatment of clinical symptoms. Studies focusing on the dopamine system have purported the hypothesis of a dopamine imbalance in mesocorticolimbic circuit, i.e., either excessive subcortical dopamine or deficient prefrontal dopamine will cause schizophrenia symptoms. However, it is clear that drugs specifically targeting dopamine receptors are not sufficient for the treatment of schizophrenia. Novel approaches are urgently needed. Recent studies have proposed that schizophrenia is closely associated with interacting abnormalities of both the dopamine and glutamate systems. Indeed, besides dopamine, several lines of evidence support the hypothesis of the persistent dysfunction of glutamatergic transmission, especially *N*-methyl-D-aspartate (NMDA) receptors, in the pathogenesis of schizophrenia. In the past decade, a number of studies have shown that the function of aberrant NMDA receptors may underlie many aspects of molecular, cellular, and behavioral aberrations associated with schizophrenia. We review the current literature and explain the onset and

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pathogenesis of schizophrenia from basic and translational perspectives. Understanding the neurogenesis and neurobiological basis is important in the development of more effective intervention strategies to treat or prevent this devastating disorder.

Keywords: Prefrontal cortex, dopamine, glutamate, NMDA receptors, psychiatric disorders, schizophrenia

1. INTRODUCTION

Schizophrenia is a complex psychological disorder with neurological components first described in 1887 as dementia praecox by German physician Emil Kraepelin. Schizophrenia consists of a complex set of positive, negative, and cognitive symptoms. Positive symptoms reflect an excess or distortion of normal functions. These active, abnormal symptoms include delusions, hallucinations, thought disorder, and disorganized behavior. Negative symptoms refer to a diminishment or absence of characteristics of normal function. They may appear months or years before positive symptoms. They include loss of interest in everyday activities, apparent lack of emotion, reduced ability to plan or carry out activities, neglect of personal hygiene, social withdrawal, and loss of motivation. Cognitive symptoms, which involve problems with thought processes, may be the most disabling in schizophrenia, because they interfere with the ability to perform routine daily tasks. A person with schizophrenia may be born with cognitive symptoms, but they may worsen when the disorder starts. They include problems with making sense of information, difficulty paying attention, and problems with memory. Schizophrenia can also affect mood, causing depression or mood swings, that is, affective symptoms. In addition, people with schizophrenia often seem inappropriate and odd, causing others to avoid them, which further leads to social isolation. Given the serious nature of this disease, much research has been conducted over the past century to better understand schizophrenia. One area of intense research involves understanding how neuronal chemicals in the brain, such as dopamine and glutamate, impact schizophrenia.

For more than 50 years, the dopamine hypothesis has dominated the theories of schizophrenia. Hyperactivity in the mesolimbic dopamine pathway is specifically proposed as the mediator of positive symptoms of schizophrenia. More recently, hypoactivity in the mesocortical dopamine pathway is hypothesized to be the mediator of negative, cognitive, and affective symptoms of schizophrenia. However, in the past two decades, hypotheses of schizophrenia have progressed beyond the dopamine hypothesis of overactive mesolimbic dopamine neurons and underactive mesocortical dopamine neurons. A major hypothesis of schizophrenia proposes that numerous genetic risk factors converge on the *N*-methyl-D-aspartate (NMDA) receptor for the neurotransmitter glutamate. Theoretically, neurodevelopmental abnormalities in glutamate synapse formation result in the hypofunction of NMDA receptors. Since NMDA receptors regulate dopamine neurons, the hypofunction of NMDA receptors may be responsible for the abnormal dopamine activity associated with the symptoms of schizophrenia. In this chapter, we review the current literature, elaborate the formulations of hypotheses of schizophrenia, and explain what is known about the onset and pathogenesis of schizophrenia from basic and translational perspectives.

2. THE DOPAMINE HYPOTHESIS

2.1. Evolution of Dopamine Hypothesis

The idea that dopamine and dopaminergic mechanisms are central to schizophrenia, particularly psychosis, has been one of the most plausible and established hypothesis about the illness. This hypothesis evolved from clinical observations, received empirical validation from antipsychotic treatment, and gained support from direct imaging studies. Although the dopamine hypothesis remains insufficient to clearly explain the complexity of this devastating disorder, it offers a direct relationship to symptoms, particularly positive symptoms, and to their treatment. Van Rossum in 1966 proposed the first dopamine hypothesis of schizophrenia, i.e., hyperactivity of dopamine transmission was responsible for the disorder [1]. This hypothesis was based largely on the observations that psychostimulants that increase dopamine levels can activate dopamine receptors and cause psychosis, whereas antipsychotic drugs that decrease dopamine levels can treat psychosis by blocking dopamine D_2 receptors [2]. Much of the evidence was derived from the original work of Arvid Carlsson, who characterized the presence of dopamine in the brain and the effects of neuroleptics on dopaminergic systems [3]. This classical dopamine hypothesis received further support from the correlation between clinical doses of antipsychotic drugs and their potency to block D2 receptors [4, 5] and from the psychotogenic effects of dopamine-enhancing drugs [6-9]. Given the predominant localization of dopamine terminals and D2 receptors in subcortical regions such as the striatum and the nucleus accumbens, this dopamine hypothesis of schizophrenia mainly focused on subcortical regions.

Although this intriguing hypothesis was initially supported by a large body of evidence, it was clear that dopamine metabolites, which reflect cortical dopamine metabolism, were not universally elevated in the cerebrospinal fluid (CSF) or serum of patients with schizophrenia [10]. In fact, dopamine metabolites were reduced in some patients with schizophrenia even though the patients showed severe symptoms and responded to antipsychotic drugs. The focus on D2 receptors was also brought into question by findings showing that clozapine had superior efficacy for patients who were refractory to other antipsychotic drugs despite the fact that clozapine has relatively low affinity and occupancy at D2 receptors [11-13]. Furthermore, the postmortem studies of D2 receptors in patients with schizophrenia could not exclude the confounding effects of previous antipsychotic treatment. Some positron emission tomography (PET) studies of D2/3 receptors in drug-naive patients showed contradictory results [8]. Taken together, these findings were incompatible with the simple hypothesis of excess subcortical dopamine transmission.

Furthermore, the importance of enduring negative and cognitive symptoms in this illness and of their resistance to D2 receptor antagonism was becoming increasingly noteworthy. This change in emphasis led to a reformulation of the classical or early version of the dopamine hypothesis [7, 8, 14-16]. Many preclinical and clinical studies documented the importance of prefrontal dopamine transmission at D1 receptors for optimal prefrontal cortex performance [15, 17-21]. Functional brain imaging studies suggested that the cognitive and negative symptoms might arise from altered prefrontal cortex functions [22]. Lesions of either midbrain cell bodies in the ventral tegmental area or of frontal cortical areas directly, with subsequent loss of dopamine terminals from the medial prefrontal cortex, induced

hyperactivity in rats and enhanced behavioral responses to amphetamine, whereas a lesion of the subcortical dopamine pathways resulted in the opposite effects [23, 24]. These data suggested that prefrontal dopamine activity exerts an inhibitory influence on subcortical dopamine activity [23-27]. However, it was imaging studies, which showed reduced cerebral blood flow in frontal cortex, that provided the best evidence of hypofrontality and regional brain dysfunction in schizophrenia [28]. Because CSF dopamine metabolite levels reflected cortical dopamine metabolism, the relationship between hypofrontality and low CSF dopamine metabolite levels indirectly suggested a possible low frontal dopamine level. This idea provided a mechanism for proposing that schizophrenia is characterized by frontal hypodopaminergia that may cause striatal hyperdopaminergia.

Together, these observations led to the hypothesis that a deficit in dopamine transmission at D1 receptors in the prefrontal cortex might be implicated in the cognitive impairments and negative symptoms of schizophrenia [7, 29], whereas the excess dopamine transmission in the striatum may be related to the positive symptoms. The major innovation of this hypothesis was the move from a one-sided dopamine hypothesis explaining all facets of schizophrenia to a regionally specific prefrontal hypodopaminergia and a subcortical hyperdopaminergia. Consequently, an imbalance in dopamine with hyperactive subcortical mesolimbic projections, causing hyperstimulation of D2 receptors and positive symptoms, and hypoactive mesocortical dopamine projections to the prefrontal cortex, causing hypostimulation of D1 receptors, negative symptoms, and cognitive impairment, became the predominant hypothesis in the past 20 years (Figure 1).

The main area of progress was the addition of regional specificity to the hypothesis to account for the available postmortem and metabolite findings, imaging data, and new insights from animal studies into cortical-subcortical interactions. Although it is a substantial advance, the dopamine hypothesis has a number of weaknesses as well. Much of the evidence for the hypothesis relied on the results from animal studies or other clinical conditions. There was still no direct evidence of reduced dopamine levels in the frontal cortex and limited direct evidence for elevated striatal dopaminergic function. In fact, recent evidence suggested that the dopamine system may be "normal" in its configuration but instead is abnormally regulated by modulatory processes [30]. It was also unclear how the dopaminergic abnormalities were linked to the clinical phenomena. For example, there was no framework describing how striatal hyperdopaminergia translates into delusions or how frontal hypodopaminergia results in blunted affections. Furthermore, it has become clear that the cortical abnormalities are more complicated than the proposed hypofrontality or cortical hypodopaminergia [31, 32], as we discuss in Section 3 below. More importantly, this classical hypothesis ignored neurodevelopmental and prodromal aspects of schizophrenia, did not describe the etiological origins of the dopaminergic abnormality, did not pinpoint which element of dopaminergic transmission was abnormal, and did not mechanistically address how cortical hypodopaminergia and striatal hyperdopaminergia would occur.

2.2. Novel Evidence for an Integrated Hypothesis

Much has changed since the dopamine hypothesis was first formulated. Many critical data, as exhibited below, have emerged to support a new integrated hypothesis for

schizophrenia, i.e., dopamine dysfunction as a final and common end point for the illness [8, 16].

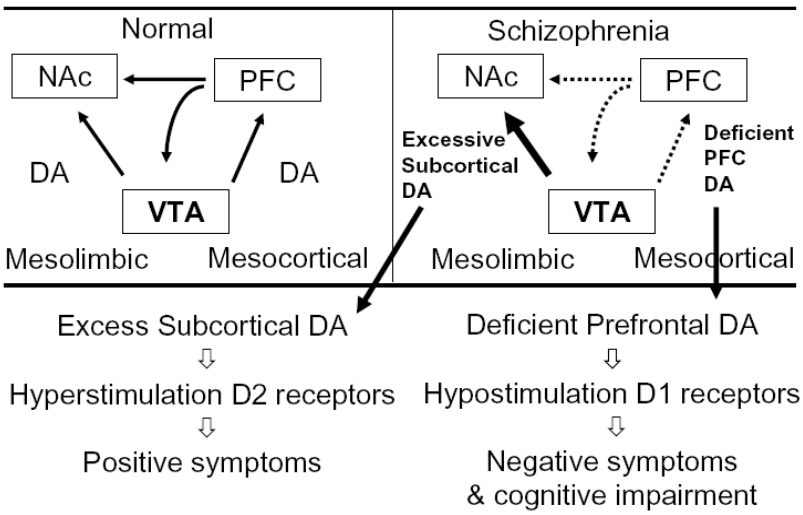

Figure 1. Dopamine imbalance hypothesis of schizophrenia. DA: dopamine, NAc: nucleus accumbens, PFC: prefrontal cortex, VTA: ventral tegmental area.

2.2.1. Neurochemical Imaging of Schizophrenia

Although it is not possible to measure dopamine levels directly in human brains, techniques have been developed to provide indirect indices of dopamine synthesis, release, and putative synaptic dopamine levels. Presynaptic striatal dopaminergic function can be measured using radiolabeled L-dopa, which is converted to dopamine and trapped in dopamine nerve terminals. Using this technique, most of the studies conducted in patients with schizophrenia have reported significantly elevated presynaptic striatal dopamine synthesis capacity [33-40]. Evidence in line with this comes from a SPECT study using a dopamine depletion technique by which it is reported that baseline occupancy of D2 receptors by dopamine in the striatum is increased in schizophrenia [41-47]. In addition, by using various radiotracers, PET and SPECT studies have provided imaging of dopamine D2/3 receptors in patients with schizophrenia, albeit the findings were inconsistent. Some reported increased D2/3 receptor binding in the striatum [48-50], whereas others found no difference from controls [51, 52] or a possible decrease in D2/D3 receptors in extrastriatal areas such as the thalamus and anterior cingulate [53-56]. Further studies indicated that the D2 receptor exists in two states, i.e., high and low, and that D2-high was particularly altered in patients with schizophrenia [57-61]. Thus, dopamine D2 receptors continue to dominate and remain necessary for antipsychotic treatment, at least until a nondopaminergic antipsychotic drug is discovered [62, 63].

2.2.2. The Genetic Etiology of Schizophrenia

After many years of intensive investigations, it is unfortunate that no single gene was found to be able to encode for schizophrenia. Rather, a number of high-risk genes are associated with schizophrenia [64]. In fact, 4 of the top 10 gene variants most strongly associated with schizophrenia are directly involved in dopaminergic pathways, including the

catechol-o-methyltransferase gene (*COMT*) [14, 65-70], neuregulin 1 (*NRG1*) [71, 72], DISC1 [73, 74], and dysbindin [75-78]. Many of the other gene variants in the top list are involved in brain development, such as reelin, or influence more ubiquitous brain transmitters such as glutamate or γ-aminobutyric acid (GABA) [64, 78-83]. Although recent findings have generated great interest in the copy number variations in schizophrenia, they are rare and are unlikely to account for the majority of cases of schizophrenia. Instead, most of them are likely to be susceptibilities [64, 84, 85]. Of the ones that have been identified, some have already been tied to altered dopamine transmission, but the functional relevance of most of them to dopamine function is not known [86].

2.2.3. Environmental or Epigenetic Risk Factors for Schizophrenia

A large number of disparate environmental factors contribute to the risk for schizophrenia. Markers of social adversity such as migration, unemployment, urban upbringing, lack of close friends, and childhood abuse are all associated with a well-established increased risk for schizophrenia that cannot readily be explained by genetic factors [87-89]. Studies in animals of social isolation [90-92] and subordination [90, 93] find that these factors lead to dopaminergic hyperactivity. Other environmental factors, such as pregnancy/obstetric complications, act in early life to increase the subsequent risk of schizophrenia [94-96]. There is now substantial evidence from animal models that pre- and perinatal factors can lead to long-term hyperactivity in mesostriatal dopaminergic function [30, 97-99]. For example, neonatal lesion of the hippocampus [100-102] or frontal cortex [103, 104] increases dopamine-mediated behavioral responses in rats [105-108]. Neonatal exposure to toxins also leads to increased dopamine-mediated behavioral responses [109] and elevated striatal dopamine release [110]. Prenatal and neonatal stress, such as maternal separation, also increases striatal dopamine metabolism [103] and release [111, 112].

A number of psychoactive substances also increase the risk of schizophrenia. The relationship between psychostimulants and psychosis and their effects on dopaminergic function has long been emphasized [113, 114]. For example, cannabis use has recently emerged as a risk factor for schizophrenia [115, 116]. The main psychoactive component of cannabis has been shown to increase striatal dopamine release via activation of cannabinoid receptors [117-120]. Psychoactive drugs acting on other systems may also act indirectly on the dopaminergic system by potentiating dopamine release. For example, the NMDA receptor blocker ketamine, as well as phencyclidine (PCP) and dizocilpine (MK-801), was found to increase amphetamine-induced dopamine release in healthy humans to the levels seen in patients with schizophrenia [121-125].

2.2.4. Prodrome to Psychosis: Schizophrenia as a Neurodevelopmental Disorder

It is increasingly recognized that schizophrenia is a neurodevelopmental disorder that involves disrupted alterations in brain circuits [29, 126, 127]. Although psychosis always emerges in late adolescence or early adulthood, we still do not understand all of the changes in normal or abnormal development prior to and during this period. It is particularly unclear what factors alter the excitatory-inhibitory synaptic balance in the juvenile and what changes induce the onset of cognitive dysfunction. Current studies suggest that problems related to schizophrenia are evident much earlier. The emerging picture from genetic and epigenetic studies indicates that early brain development is affected. Many of the structural variants associated with schizophrenia indicate that neurodevelopmental genes or epigenetic factors

are involved with neuronal development [73, 128-130]. These findings, although intriguing, are limited in that they do not reveal the changes that occur before psychosis. At present, the diagnosis of schizophrenia is based primarily on the symptoms and signs of psychosis. It has recently been proposed that schizophrenia may progress through four stages: from risk to prodrome to psychosis to chronic disability [131]. Obviously, the key to preventing or forestalling the disorder is to detect early stages of risk and prodrome. Therefore, the need is urgent to identify novel biomarkers and new cognitive tools as well as subtle clinical features for early diagnosis and treatment [131, 132].

Significant neurobiological research in recent years has focused on the early signs or prodrome of the illness and on the subtle manifestations of symptoms within family members and the population in general [133-135]. These groups are at increased risk of schizophrenia but have not yet developed the illness. Evidence from studying these groups therefore has the potential to provide information about the causal chain of events leading to the development of schizophrenia. Individuals meeting clinical criteria for a high risk of psychosis are likely to develop schizophrenia within the following few years [135]. Before psychosis appears, they have already shown elevated striatal dopamine transmission that is positively associated with symptom severity in patients with schizophrenia [38]. Elevated presynaptic striatal dopaminergic function is also seen in other groups with an increased risk of developing psychosis [136] and in the relatives of people with schizophrenia. They also show higher dopamine metabolite levels in response to stressors than healthy controls [137] and an association between greater changes in dopamine metabolite levels with higher levels of psychotic like symptoms following stress [138]. Overall, these findings indicate that dopaminergic abnormalities are not just seen in people who are frankly psychotic but are also seen in people with risk factors for psychosis, who often have signs and symptoms, although at a less severe level. Furthermore, stress in these individuals has been linked to both an increase in these symptoms and an increase in dopaminergic indices [88].

2.2.5. Interactions between or among Risk Factors and a Common Dopamine Pathway for Schizophrenia

Genes and environmental factors, as discussed above, do not exist in isolation. Many interact with each other, and some show synergistic effects on the risk of schizophrenia or brain abnormalities associated with schizophrenia [14, 139-141]. Furthermore, animal studies indicate that at least some of these factors interact to affect dopamine systems [142-144]. Interactions between gene variants, including those influencing dopaminergic function, and environmental risk factors are another possible route to dopaminergic dysfunction. This idea is illustrated by findings that variants of the *COMT* interact with early cannabis exposure to increase the subsequent risk of psychosis [145] and, in other studies, to increase paranoid reactions to stress [88]. Family history of psychosis also interacts with environmental factors to increase the risk of schizophrenia [146, 147]. As reviewed above, animal studies indicate that frontal dysfunction can increase striatal dopamine release. Animal studies, particularly developmental models such as gestational exposure to methylazoxymethanol acetate (MAM) and other high-risk genes (*DISC1, NRG1,* dysbindin,), will certainly help to reveal the neurodevelopmental trajectory of schizophrenia, yield disease mechanisms, and eventually offer opportunities for the development of new treatments [30, 99, 148]. On the basis of insights from animal research about normal brain development, it is proposed that the appearance of diagnostic symptoms is linked to the normal maturation of brain areas affected

by the early developmental pathological processes [149-151]. The course of the illness and the importance of stress and other risk factors may be related to normal maturation of dopaminergic neural systems, particularly those innervating prefrontal cortex and striatum.

Although further work is clearly needed to investigate the nature and extent of all of these possible interactions, the evidence indicates that many disparate, direct, and indirect environmental and genetic factors may lead to dopamine dysfunction. As the dopamine hypothesis evolves, the scientific challenge will be not just to find predisposing genes but also to articulate how genes and environment interact to lead to dopamine dysfunction. In fact, several recent studies of different high-risk genes for schizophrenia, including dysbindin, *DISC1*, and *NRG1*, have consequently resulted in dopaminergic dysfunctions [71, 73, 75, 76], although the exact mechanisms associated with these changes remain to be explored.

An attractive feature of the dopamine hypothesis is that it proposes a dysfunction in the dopamine system as a complete explanation for schizophrenia: a prefrontal hypodopaminergia leading to a subcortical hyperdopaminergia. However, there is little convincing evidence for this sequence of events related to dopamine dysfunction. On the other hand, substantial evidence indicates that multiple routes (genetic, neurodevelopmental, environmental, social) lead to the striatal hyperdopaminergia, as discussed above. As a result, it has been proposed that both dopamine imbalance models are mutually correlated because a deficiency in mesocortical dopamine function may translate into disinhibition of mesolimbic dopamine activity [29]. It should be noted that recent data suggest that these frontal/cognitive changes need not necessarily be primary but instead may arise as a consequence of striatal dysfunction [16, 152, 153]. Thus, in contrast to the classical dopamine hypothesis, recent advances propose that changes in multiple transmitter/neural systems underlie the cognitive dysfunction and negative symptoms of schizophrenia, and in many cases these dysfunctions precede the onset of psychosis. It is when these pathways converge with other biological or environmental influences and lead to striatal dopamine hyperfunction that psychosis becomes evident and the diagnosis of schizophrenia is able to be confirmed.

Flowchart 1 Hypothesis of the pathophysiological process leading to schizophrenia
Etiology: multiple factors such as DNA, gene expression, viruses, toxins, birth injury, stress, psychological experiences et al ⇒ Pathophysiology: brain development from conception to early adulthood (e.g., neuron formation, synaptogenesis, synaptic pruning, activity-dependent changes of enzymes, ion channels, and receptors) ⇒ Anatomical and functional disruption in neuronal connectivity and communication ⇒ Dopaminergic dysfunction and impairment in cognitive processes (e.g., attention, memory, emotion) ⇒ Symptoms of schizophrenia (e.g., cognitive, negative, positive, and affective symptoms).

In summary, as shown in Flowchart 1, multiple environmental and genetic risk factors interact to evolve into a final common pathway of presynaptic D2 receptor-associated striatal hyperdopaminergia. Furthermore, the pathway provides a framework linking the abnormal neurochemical processes to symptoms and explains why many disparate risk factors and functional and structural abnormalities are associated with schizophrenia. In addition to guiding us through dopamine dysregulation, the multiple environmental and genetic risk factors influence diagnosis by affecting other aspects of brain function that underlie negative and cognitive symptoms. Schizophrenia is thus the result of dopamine dysregulation in the context of a compromised brain.

3. GLUTAMATE HYPOTHESIS OF SCHIZOPHRENIA

As discussed above, hypotheses of schizophrenia have progressed beyond the dopamine hypothesis of overactive mesolimbic dopamine functions and underactive mesocortical dopamine transmission. In a major breakthrough on the etiology of schizophrenia, it has been proposed that numerous genetic risk factors, as discussed above, converge on the NMDA receptors for the neurotransmitter glutamate. Theoretically, neurodevelopmental abnormalities in glutamate synapse formation result in the hypofunction of NMDA receptors. Indeed, genetic inactivation of NMDA receptors in ventral tegmental area dopamine neurons results in specific behavioral modifications associated with drug-seeking behaviors and significantly attenuates phasic dopamine release in the adult animals following the delivery of a reward [154, 155]. Because NMDA receptors regulate dopamine neurons and dopamine transmission, the hypofunction of NMDA receptors may be responsible for the abnormal dopamine activity associated with the symptoms of schizophrenia.

3.1. The NMDA Receptor is Important for Cognitive Functions and Is Subject to Dopaminergic Regulation

Glutamate receptors are classified into ionotropic and metabotropic receptors. The former include NMDA, kainate, and AMPA subtypes whereas the metabotropic glutamate receptors are composed of mGlu1-8 and modulate neurotransmission by activating G protein-coupled synaptic transduction mechanisms. The NMDA receptor has long been associated with learning and memory processes and with diseased states in psychiatric disorders [156]. The NMDA receptor is a heteromeric complex formed by an assembly of subunits, with an obligatory subunit NR1 and a combination of NR2A-D and/or NR3A-B subunits. It is permeable to Ca^{2+} and is uniquely gated by both voltage and ligands (Figure 2A). The biophysical and pharmacological properties of the NMDA receptor are greatly impacted by the changes in NR2 and NR3 subunits and by binding sites of glycine, PCP, and Mg^{2+}. It is well known that the maturation of brain circuitry is usually coincident with the NMDA receptor subunit switch that occurs at the onset of the critical period of cortical development [157-160]. The differential regulation of NMDA receptor subtype expression with respect to brain areas and cell types exerts an important function in the developmentally regulated change of neuronal plasticity. The switch from 'young' to 'adult' forms of NMDA receptors during corticolimbic development makes it extremely vulnerable to environmental or epigenetic risk factors. The NMDA receptor subunit shift therefore marks the transition from juvenile to “adult” neural processing in many brain regions [161, 162]. Multiple lines of evidence suggest that the prepuberty period produces brain region-specific changes in NMDA receptor activity and that NMDA receptor sensitivity to psychostimulants and stress reaches the highest level [163, 164]. We propose that the normal expression of NMDA receptors in the prefrontal and hippocampal neurons is critical for normal operation of cognitive functions. Indeed, either overexpression or knockdown/knockout of individual NMDA receptor subunits in the forebrain dramatically affects cognitive functions [160, 165-168].

Although the mechanisms involved in the switch of NR2B to NR2A remain unclear, recent studies have provided interesting findings related to NMDA receptor subunit trafficking, including phosphorylation, insertion (exocytosis), and internalization (endocytosis). All of these processes are regulated by dopamine via activations of D1 stimulation in the striatal neurons [169-172]. Our recent data indicated that D1 activation potentiates NMDA receptor-EPSCs by inserting NR2B subunits into the membrane surface in the prefrontal neurons and that this action is PLC–PKC–Src dependent [173, 174]. Because NR2B subunits exhibit much higher surface mobility and endocytosis than other NMDA receptor subunits [175-177], the higher proportion of NR2B expression in the prefrontal neurons [178] makes the prefrontal synapses more plastic and vulnerable to detrimental stimulation. Indeed, hyperdopamine stimulation initiates the switch by internalizing NR2B subunits and thus affects neuronal communication through D2 receptor-mediated activation of Akt-GSK-3β pathway in the prefrontal cortex [179]. In this context, the higher fraction of NR2B appears to be a two-edged sword for the prefrontal neurons. On one hand, higher levels of NR2B are needed for normal prefrontal functions [166] and for learning flexible behaviors; on the other hand, neurons with more NR2B are more fragile and vulnerable to excess glutamate release and dopamine stimulation [179-183] [173]. This intriguing hypothesis, yet to be tested, seems to fit well with the vulnerability of prefrontal functions in the adolescent brain. Indeed, increased levels of NR2B in the frontal cortex of juvenile mice affect anxiety- and fear-related behaviors [184], whereas blockade of NR2B subunits in the cingulate cortex impairs the formation of contextual memory [166].

Increasing evidence indicates that concurrent alterations of dopamine and NMDA receptor function play a critical role in the pathophysiology of schizophrenia. The current hypothesis postulates NMDA receptor hypofunction and cortical/subcortical dopamine imbalance for the pathophysiology of schizophrenia [185]. However, evidence in support of this hypothesis is still limited, and many of these speculations remain to be tested [127, 186]. Whether and how NMDA receptor hypofunction induces dysfunction of dopamine, or vice versa, in the prefrontal cortex and other limbic brain regions remain to be tested.

3.2. Glutamatergic–GABAergic Interactions and NMDA Receptor Hypofunction in Schizophrenia

In the past two decades, the abnormalities found in schizophrenia and the various models of schizophrenia in humans and animals all point to an important contribution of the glutamate and GABA system to the disease [187-189]. Accumulating studies have shown that aberrant NMDA receptor function may underlie many aspects of molecular, cellular, and behavioral abnormalities associated with schizophrenia [187, 190]. Recent evidence increasingly supports the hypofunction of NMDA receptors in the limbic brain region in the pathophysiology of schizophrenia [167, 187, 188, 190-194]. First, NMDA receptor antagonists, such as PCP, MK-801, and ketamine, produce "schizophrenia like" symptoms in healthy individuals [195-197]. Second, a majority of the genes that are associated with an increased risk for schizophrenia can influence the function of NMDA receptors or related receptor-interacting proteins and signal transduction pathways [14, 198]. Third, dysregulated NMDA receptor subunits are usually seen in postmortem tissue from patients with schizophrenia [199-201] and in animal models of NMDA receptor antagonism [202, 203].

Postmortem studies also show changes in glutamate receptor binding, transcription, and subunit protein expression in the prefrontal cortex, thalamus, and hippocampus of subjects with schizophrenia [204]. These changes include decreased NR1, increased excitatory amino-acid transporter, and altered NMDA receptor-affiliated intracellular proteins such as PSD95 and SAP102 in the prefrontal cortex and thalamus. Fourth, glutamatergic neurons also interact with other neurons that have been strongly implicated in the pathophysiology of schizophrenia, including morphologically altered GABAergic interneurons [205] and antipsychotic drug-targeted dopamine neurons. Moreover, mice with reduced NMDA receptor expression also display behaviors related to schizophrenia [167].

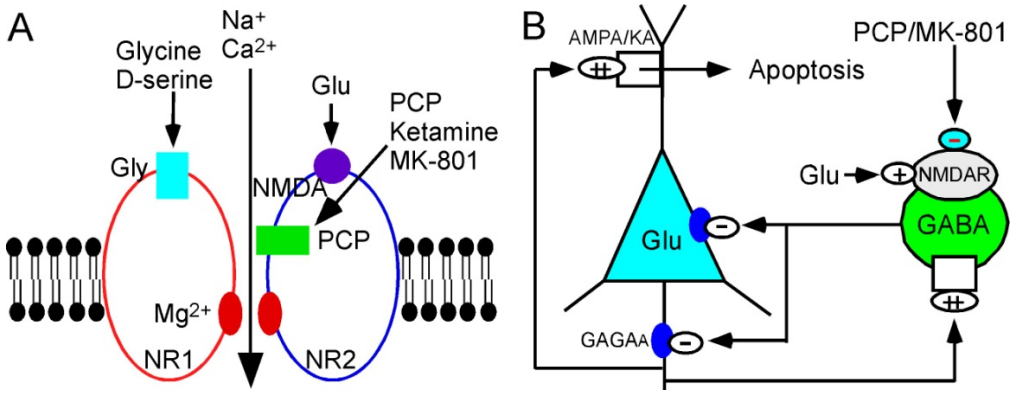

Figure 2. Hypothesis of NMDA receptor hypofunction. A, Schematic diagram of NMDA receptor complex. B, NMDA receptor hypoactivity and glutamate neurotoxicity. PCP/MK801 ⇒ NMDA receptor hypofunction on GABAergic neurons ⇒ disinhibition of pyramidal neurons ⇒ more glutamate release ⇒ AMPA/KA receptors excessively stimulated ⇒ excitotoxic damage.

On the basis of these observations, it has been postulated that the glutamatergic disturbances may involve hypofunctioning of NMDA receptors on GABA interneurons [192, 202, 206, 207]. Compelling evidence has suggested that the NMDA receptor antagonist PCP and its analogue compounds can produce a pattern of metabolic, neurochemical, and behavioral changes that reproduce almost exactly those seen in patients with schizophrenia, with remarkable regional specificity [208]. This finding has provided considerable insight into the processes that lead to the development of the disease, emphasizing the potential importance of NMDA receptor hypofunction. How might this be achieved? Activity in the corticolimbothalamic circuit is strongly regulated by local GABAergic interneurons, especially basket and chandelier cells. Output from the cortical pyramidal neurons is suppressed and coordinated by GABAergic interneurons. These cells are activated by recurrent collaterals from the pyramidal neurons and exert a powerful feedback inhibitory action on pyramidal cells via synapses onto the soma and axon hillock (Figure 2B). Both basket and chandelier cells are particularly important for restraining excessive pyramidal neuron activity, which leads to dramatic disinhibition of the pyramidal neuron efferent activity and elevated uncoordinated firing throughout the corticolimbic circuit (Figure 2B). Considering the dysfunction of NMDA receptor subunits in patients with schizophrenia [200, 201, 204, 209-212], it has been speculated that NMDA receptor subunits, particularly the NR2A subunit, distributed on interneurons may be responsible for NMDA receptor hypofunction. The central pathological characteristics seem to be caused by NMDA receptor

hypofunction acting on GABAergic interneurons, followed by the disinhibition of glutamatergic transmission and an overstimulation of non-NMDA receptors on pyramidal neurons (Figure 2B) [192, 202, 206, 207].

The question is by what mechanism and when does the hypofunction of NMDA receptor occur. It would be important to find out which neurons express altered glutamate receptor subtypes, whether these neurons are inhibitory or excitatory, and how the circuitries are affected. We propose a heuristic model for the pathophysiology of schizophrenia that attempts to reconcile the neuropathological and neurocognitive features of the disorder. We hypothesize that the hypofunction of the NMDA receptor on GABAergic interneurons disrupts the functional integrity of the corticolimbic circuit, causing cognitive impairements and negative symptoms. The resultant disinhibition of glutamatergic efferents and increased glutamate release cause neurotoxicity and symptoms related to schizophrenia. The hypothesis obviously depends on the differential NMDA receptor sensitivity to NMDA receptor antagonists on the GABAergic interneurons. The result of these hypothesized mechanisms is excessive stimulation of the glutamate receptor complexes. In turn, this excessive stimulation could lead to disruption of ionic equilibrium across neuronal membranes, cell death, and other mechanisms, particularly on the dopamine systems. The postulated existence of disinhibited glutamatergic transmission and the subsequent cascade of excitotoxic events resulting from NMDA receptor hypofunction, degeneration of GABAergic interneurons, or a combination of both, have suggested diverse experimental therapeutic interventions for schizophrenia, such as facilitation of NMDA receptor-mediated neurotransmission and potentiation of GABAergic inhibition and antagonism of AMPARs [188, 213].

In summary, this review of previous studies has provided convincing evidence of hypofunction of a subset of GABAergic interneurons and hypofunction of NMDA receptors in the prefrontal cortex of patients with schizophrenia. Are these two separate and distinct pathological mechanisms or can they be related to each other in some meaningful pattern? Previous findings suggest a particular vulnerability of GABAergic interneurons to the effects of NMDA receptor antagonists. On the basis of these findings, it is reasonable to speculate that the NMDA receptors on frontal cortical and limbic GABAergic interneurons are most sensitive to these antagonists and therefore may be an important site of pathology resulting in NMDA receptor dysfunction. However, many questions remain to be answered. For example, in the cortical circuitry consisting of both pyramidal cells and interneurons, why do PCP and its analogue compounds selectively act on a subset of interneurons, i.e., parvalbumin-containing, fast-spiking interneurons? Are NMDA receptor properties on interneurons different from those on pyramidal cells? On the basis of the “disinhibition” hypothesis, does PCP directly depress excitatory transmission between the pyramidal cell and the interneuron? How does PCP affect the inhibitory transmission on pyramidal cells and what effect does it have on different glutamatergic inputs such as corticocortical and thalamocortical synapses on interneurons and pyramidal cells, respectively? Under the condition of hypothesized hypofunctional NMDA receptors, such as subchronic or chronic PCP/MK-801 treatment, how would the excessive release of glutamate lead to excitotoxicity in the interneurons? Would dysfunction of NMDA receptors consequently result in dopamine dysfunction as proposed above? Obviously, it is important to answer these questions as the first step, followed by identification of their downstream signaling pathways [214] and their close relationships with the possible involvement of dopamine D2 receptors. To address these questions, we recently reported cell type-specific development of NR2 subunits in pyramidal neurons and

GABAergic interneurons of rat prefrontal cortex [178, 215]. NR2B levels remain high until adulthood, without significant NR2B-to-NR2A subunit switch, in layer 5 pyramidal neurons; however, they are gradually replaced by NR2A subunits in fast-spiking interneurons [215]. These basic studies in NMDA receptor development in the prefrontal cortex have been extremely useful in the formulation of an NMDA receptor hypofunction hypothesis.

As discussed above, we propose that dysfunction of NMDA receptors in the dopamine neurons and GABAergic cells induces dopamine hyperactivity or GABA downregulation, which in turn results in psychosis. Given that both dopamine and GABA systems are indeed the targets of NMDA receptor disruption, our hypothesis is certainly plausible.

4. CONVERGENCE OF THE DOPAMINE HYPOTHESIS WITH OTHER MAJOR HYPOTHESES IN SCHIZOPHRENIA

The original dopamine hypothesis of schizophrenia proposed that hyperactivity of dopaminergic transmission leads to the symptoms of schizophrenia [3]. This hypothesis was supported by the observation that all antipsychotic drugs blocked D2 receptors [4, 216]. Imaging studies provided more direct evidence for the dopamine hypothesis, suggesting hyperfunction of the striatal dopamine system. These studies found increased uptake of L-dopa, increased amphetamine-induced dopamine release, and increased occupancy and density of D2 receptors in the striatum [8, 45, 49].

On the other hand, another deficit, a hypofunction of the prefrontal cortex, has been associated with the cognitive symptoms. The nature of this hypofunction is unclear, but hypofunctioning of both the dopamine system and the GABAergic system has been postulated to account for this cognitive deficit [14, 127]. Although the evidence for dopaminergic hypofunction in the prefrontal cortex is not yet substantial [15, 217-219], several studies have found decreased expression of GABAergic markers in the cortex, including the prefrontal cortex [205, 220-222]. These findings raise the important question: Are cortical GABAergic hypofunction and subcortical dopaminergic hyperfunction related? Indeed, they are. We recently found that overexpression of dopamine D2 receptors in the striatum leads to decreased inhibitory GABAergic synaptic transmission and shifted dopamine sensitivity in the mouse prefrontal cortex [223]. Furthermore, hypotheses of schizophrenia have progressed beyond the dopamine hypothesis. An additional factor supporting the evidence for dopamine dysregulation in schizophrenia is its plausibility in the overall context of other transmitter systems that may be altered in schizophrenia, in particular with the NMDA hypofunction hypothesis. More specifically, imaging studies have shown that NMDA hypofunction can lead to dopamine alterations similar to those observed in schizophrenia, namely, subcortical dopamine excess and cortical D1 upregulation [121, 224]. More recently, neurodevelopmental abnormalities in glutamate synapse formation have resulted in the hypofunction of NMDA receptors, which in turn may result in abnormal dopamine activity associated with psychosis and the symptoms of schizophrenia. Such convergence suggests that the main neurochemical dysregulations described in schizophrenia are not mutually exclusive. Glutamatergic and GABAergic alterations in schizophrenia could be linked and could lead to or could be associated with inefficient control of cortical input onto subcortical striatal dopamine and inefficient corticocortical connectivity and function.

Dopamine dysregulation may be the end point of a cascade of upstream events, an end point for psychosis that is most directly associated with the major symptoms of the illness and their treatment [57]. Therefore, future drug development should focus on the systems acting on the signaling pathways or neurochemicals that lead to the final common dopamine pathway instead of on the dopamine D2 receptor alone.

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