Full-length review

An integrated view of pathophysiological models of schizophrenia

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Abstract

Pathophysiological processes that underlie the profound neuropsychiatric disturbances in schizophrenia are poorly understood. However, the clinical course of the disease, and a number of clinical and basic science observations, provide direction for formulating pathophysiological models that could be empirically tested. For example, repeated psychostimulant administration to healthy subjects can induce psychotic symptoms, and acute stimulant challenge in schizophrenia patients can precipitate psychosis. Also, NMDA antagonists induce positive, negative, and cognitive schizophrenic-like symptoms in healthy volunteers and precipitate thought disorder and delusions in schizophrenia patients. These human studies provide support for the dopamine and NMDA receptor hypofunction hypotheses of schizophrenia. Well-documented effects of NMDA antagonists on dopamine systems provide a basis to integrate the dopamine and NMDA receptor hypofunction hypotheses. Furthermore, it has become apparent that prominent actions of antipsychotic drugs, especially those with ‘atypical’ properties, involve antagonism of behavioral, electrophysiological and brain metabolic effects produced by administration of NMDA receptor antagonists. A confluence of clinical and basic science data suggests that an early developmental insult, potentially involving reduced NMDA receptor function, could facilitate sensitization of dopamine systems, leading to the formal onset of schizophrenia in late adolescence and early adulthood. Although clearly speculative, this conceptual model is consistent with existing evidence and suggests lines of future experimental investigation. © 1999 Published by Elsevier Science B.V. All rights reserved.

Keywords: Schizophrenia; Ketamine; NMDA; Animal model; Amphetamine; Dopamine; Stress

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1. Introduction

Identification of specific pathophysiological processes and etiologic factors in schizophrenia has proven elusive. The heterogeneity of the disorder, manifest in its highly variable phenomenology, treatment response, and illness course, complicate the formulation of theoretical models for the disease [7]. It has been postulated that the heterogeneity observed in patients with schizophrenia may be due to multiple etiologies producing different pathophysiologic mechanisms [200] or alternatively, as the result of a common etiopathogenetic process [50] explained in the context of innate constitutional differences among people [37]. In addition, environmental factors may contribute to variability in manifestations and course of the disease [127,144,154].

A debate has evolved as to whether the disease process in schizophrenia involves only neurodevelopmental pathology, or also a progressive, neurodegenerative pathophysiological component [35,36,206]. The clinical deterioration evident in the longitudinal course of schizophrenia suggests the involvement of neurodegenerative processes [45,127,136,160,223,224]. On the other hand, there is substantial evidence suggesting that neurodevelopmental pathology long precedes the formal onset of the disorder, and evolves to a static encephalopathy in schizophrenic patients [21,50,74,152,153,213].

Despite the difficulties and uncertainties in defining specific pathophysiological processes in schizophrenia, a number of consistent clinical observations provide direction for formulating models that can be empirically tested. First, psychotic symptoms can be produced in healthy subjects by repeated administration of psychostimulants [9,18]. Second, a large portion of schizophrenic patients exhibit exacerbation of psychotic symptoms in response to psychostimulants, at doses that are not psychotogenic in normals, suggesting a sensitization and supersensitivity of dopamine systems [122,124,126]. A third finding is that NMDA receptor antagonists induce schizophrenic-like symptoms in healthy subjects and precipitate psychoses in stabilized schizophrenic patients [39,44,59,115,118,119,139,141]. These latter data have led to the suggestion that schizophrenia may involve hypofunction of NMDA receptors [45,58,102,161]. Fourth, the onset of schizophrenia occurs at a certain developmental stage, with symptoms initially presenting in late adolescence or early adulthood [88,89,192]. This observation provides an important clue for modeling the disease. Fifth, as noted above, there is typically a progressive, though time-limited deterioration and accrual of morbidity in the form of positive, negative and cognitive symptoms in the longitudinal course of schizophrenia. This progression of symptom severity suggests the possibility of a pathological sensitization of neural systems [129]. Sixth, the ability of stress to precipitate the onset and relapses of schizophrenia is well documented [28,142,144]. Finally, the fact that the neuropathology of schizophrenia is of a subtle nature (in contrast to Alzheimer’s or Parkinson’s diseases) suggest that the disease may be best understood in terms of its molecular basis. The purpose of this article is to describe a hypothesis of the pathophysiology of schizophrenia that accounts for these observations. This hypothesis integrates and extends the work of other investigators [32,49,52,58,82–84,102,107,129,161,167,168] and may provide greater explanatory power for the clinical course and characteristics of schizophrenia.

2. Neurodevelopmental hypotheses of schizophrenia

Current hypotheses of schizophrenia postulate neurodevelopmental factors in the disease pathogenesis. These state that pathogenic processes (genetic or environmental) precede the formal onset of the disorder and occur in gestation or early postnatal periods. There is strong evi-
dence for a genetic component in the etiology of schizophrenia from family, twin, and adoption studies [110,199]. However, there is only a 30–50% concordance rate for schizophrenia among monozygotic twins [110], indicating that there must be epigenetic or environmental factor(s) that influences the expression of the illness. Specific etiologic factors that may be involved, independently or in combination with genetic vulnerability, include prenatal viral exposure or autoimmune reactions, [112,196] nutritional deficiency, [190] and obstetric complications [123].

Substantial evidence supports the neurodevelopmental hypotheses of schizophrenia. There have been consistent findings of persistent cytoarchitectural abnormalities in brain regions that undergo maturation during gestation and, presumably, are present at the onset of schizophrenia [2–4,19,20,100,113]. In addition, in the premorbid history of many schizophrenic patients, deficits have been noted in social, motor and cognitive functions [69,208]. The lack of any definitive evidence of neurodegeneration (e.g., gliosis [22]) and the existence of brain pathomorphology prior to and at the onset of illness, with the lack of definitive evidence of its progression [97,125,212] also suggest that neurodevelopmental pathophysiological processes precede the emergence of schizophrenic symptoms.

3. The clinical course of schizophrenia suggests patho-
logical sensitization

Evidence from studies of the longitudinal course of schizophrenia support a potential role for neurobiologic sensitization in the pathophysiology of the illness. From 30%–60% of patients experience some progression of their illness, with psychotic relapse(s) resulting in lower levels of recovery and higher levels of residual symptoms [223]. The deterioration occurs predominantly in the early stages of the illness, usually within the first five years after onset [145]. Some investigators have even suggested that the prespsychotic phase is the initial period of deterioration [37]. Kraepelin’s initial descriptions of the deteriorating course of schizophrenia are particularly relevant since they are based on observations prior to the discovery of antipsychotic drugs. Evidence for a progressive deterioration has also been found in studies of first episode schizophrenia patients who were then followed prospectively from one to five years [51,95,136,143]. Those studies found that the length of time a person experienced psychotic symptoms in their first episode of illness, prior to receiving pharmacologic treatment, was a significant predictor of the time to treatment response [127], relapse [51], and long term outcome [95,143]. Specifically, the longer the duration of psychosis the poorer the treatment response and outcome. In addition, studies that followed patients over successive psychotic episodes of illness found that some of the patients took longer to recover or, in some cases, fail to recover as they had in their previous episode [128,223,224]. It was thus postulated that psychosis might reflect a pathologic process that diminishes the ability of the patient to respond to antipsychotic medication. The pattern of clinical course is consistent with a process of pathologic sensitization [129].

4. The dopamine hypothesis of schizophrenia

4.1. Fundamental basis for the dopamine hypothesis

While aberrant neurodevelopmental processes may predispose patients to schizophrenia, the actual onset and course of the illness has been hypothesized to result from specific neurochemical disturbances in dopamine-mediated neurotransmission. The dopamine (DA) hypothesis remains the preeminent neurochemical theory of schizophrenia [55,147,186] despite certain shortcomings. The DA hypothesis was initially supported by an impressive correlation between the therapeutic doses of typical antipsychotic drugs and their binding affinity for the D2 dopamine receptor [46,177,178]. The DA hypothesis has undergone multiple revisions and has been extended to include both cortical and subcortical components [55.57,82,213,214]. In its current form, the dopamine hypothesis of schizophrenia postulates that overactivity in neurotransmission from DA cell bodies, located in the ventral tegmental area (VTA) of the midbrain, results in the development of psychotic symptoms. In addition, a hypodopaminergic state in the frontal cortical terminal fields of the mesocortical DA neurons has been hypothesized to be the basis of the ‘negative symptoms’ of schizophrenia, i.e., avolition, apathy, alogia and asociality.

4.2. Limitations of the dopamine hypothesis

There are numerous limitations of the DA hypothesis. First, no direct evidence of pathologic DA neuronal activity has been consistently demonstrated, e.g., increased levels of DA, its metabolites, or receptors, that are not potentially artifacts of antipsychotic drug treatment. Second, functional imaging studies have found no differences in the percentage of D2 receptor occupancy between responders and non-responders to antipsychotic medication [42,166]. Third, the ‘gold standard’ atypical antipsychotic drug clozapine has disproportionately low affinity for D2 receptors, in relation to the therapeutic dose of the drugs [111,179]. A distinguishing feature of clozapine and other atypical antipsychotic drugs is a relatively high affinity for 5HT2 receptors, and relatively low affinity for D2 receptors [146]. Accordingly, for therapeutic plasma levels of clozapine in humans, approximately 30–60% of D2 receptors are occupied whereas 80–90% of 5HT2 receptors are occupied in the same subjects [73,159]. By contrast, therapeutic plasma levels of haloperidol occupy 70–80% of D2
receptors [73,159]. These observations suggest that pharmacological properties other than D2 receptor antagonism account for the superior clinical efficacy of clozapine.

4.3. Clinical experience with psychostimulants as support for the dopamine hypothesis

The studies of D2 receptor occupancy by clozapine indicate that dopamine antagonistic properties of this highly effective antipsychotic drug cannot completely explain its therapeutic actions. However, the efficacy of the typical antipsychotics in many patients and studies demonstrating that dopaminergic psychostimulants can induce psychotic reactions provide compelling support for the DA hypothesis of schizophrenia. It has long been recognized that amphetamine abuse can produce symptoms that mimic positive symptoms of schizophrenia [18,114]. In addition, controlled human studies involving drug-naive volunteers have demonstrated that a psychotic state can be elicited by administration of small frequent oral doses of amphetamine [9,86]. Further evidence for stimulant-induced psychosis is documentation of consequences of the methamphetamine abuse epidemic in Japan shortly after World War II (see Ref. [175]). At that time, huge military stores of methamphetamine found their way to the open market in Japan, which led to widespread abuse. A significant number of methamphetamine abusers developed psychoses that did not resolve with discontinuation of drug use; many patients required years for recovery [175]. The chronic psychoses induced by methamphetamine abuse were clinically indistinguishable from paranoid schizophrenia.

The controlled clinical studies with stimulant administration and experience with stimulant abusers indicates that repeated administration of the drugs is required to induce psychotic symptoms. Work in experimental animals and humans has demonstrated that repeated administration of stimulants produces a behavioral sensitization to subsequent drug exposure that persists long after discontinuation of the chronic treatment [107,172,189]. This sensitization phenomenon may involve both presynaptic and postsynaptic mechanisms, since increased release of dopamine in response to methamphetamine, and increased behavioral responses to directly acting dopamine agonists have been demonstrated [5]. The progressive worsening of schizophrenic symptoms over time suggests that a sensitization process may also occur in this mental illness.

Leiberman et al. [127] have suggested potential mechanisms by which stimulant abuse could produce a chronic schizophrenic syndrome. They suggest that the initial aggravating event is enhanced dopaminergic activity that manifests as positive schizophrenic symptoms. Continued prolonged excessive dopaminergic activation is posited to induce neuronal degeneration in dopamine systems, leading to a hypodopaminergic state and negative symptoms. Indeed, chronic amphetamine treatment in rats is well documented to be toxic to dopamine nerve terminals [68,158,174]. A reduction in dopamine could result in postsynaptic receptor supersensitivity, which would explain the re-emergence of positive symptoms after transiently increased dopamine availability, as occurs during stress or exposure to dopaminergic drugs.

In support of dopamine supersensitivity in schizophrenia, studies in which dopaminergic stimulants were administered to schizophrenic patients have demonstrated enhanced behavioral and neurochemical responses in comparison to healthy subjects, suggesting a sensitization of dopamine systems. Low doses of methylphenidate induced positive symptoms in stabilized schizophrenic patients but not in controls [122,124,126]. The phenomenon appears to be state dependent in that stable, non-psychotic schizophrenia patients are less susceptible to develop transient psychosis compared to patients who have previously exhibited active psychotic symptoms [126]. DA agonist administration has also been examined as a test to predict relapse in schizophrenia [10,124]. Stable non-psychotic patients underwent provocative testing with DA agonists and then were followed prospectively after withdrawal of neuroleptic medications. Patients who had transient psychotic symptom activation had a significantly shorter time to relapse than patients who did not have symptom exacerbation. This was interpreted as a possible sign of an increased reactivity of DA neural systems in the patients who became psychotic after DA agonist stimulation [124].

Additional evidence for enhanced sensitivity of DA systems in schizophrenia comes from elegant SPECT and PET studies that have measured D2 receptor occupancy after amphetamine challenge [26,99,120,203]. Those studies involved imaging scans (SPECT or PET) after administration of competitive D2 antagonists as a radioligand, before and after acute psychostimulant administration (e.g., amphetamine, methylphenidate). The baseline scan provides a measure of D-2 receptor number in the presence of basal concentrations of synaptic DA, while the post stimulant scan provides a measure of extracellular DA that has been released in response to the stimulants. The decrement in D-2 binding between the baseline and post drug stimulation provides an index of DA release and the concentration of synaptic DA. This approach has been validated in studies of human and sub-human primates [99,203]. If sensitization occurs in schizophrenia, one possible consequence predicted is that patients would exhibit elevated levels of presynaptic and/or extracellular DA in response to stimulant challenge. Results of studies from separate groups are consistent with this hypothesis. They indicate that patients with schizophrenia have greater decrements in D-2 binding compared to control subjects, as measured by $^{125}$I – IBZM [120] or $^{11}$C – 11 raclopride [26]. However, patients in these investigations had previously received antipsychotic drug treatment, but were drug-free at the time of study. Consequently, the possibility that the results could be due to treatment effects cannot be entirely ruled
out. Nevertheless, this paradigm offers an exciting new strategy to examine a hypothesized pathophysiological mechanism in psychosis.

5. NMDA receptor hypofunction hypothesis of schizophrenia

5.1. Psychotomimetic effects of NMDA receptor antagonists in humans

In addition to altered sensitivity of DA systems in schizophrenia, there is substantial evidence to implicate alterations in NMDA receptor function as well. In early clinical studies, the cyclohexylamine anesthetics phen-cyclidine (PCP) and ketamine were observed to induce a spectrum of behavioral symptoms and cognitive deficits similar to schizophrenia [14,39,44,54,59,138]. The discovery that ketamine and PCP are NMDA receptor antagonists prompted the hypothesis that the pathophysiology of schizophrenia involves reduced NMDA receptor function [45,58,102,161]. Recent work has confirmed early clinical studies and has clearly demonstrated that subanesthetic doses of ketamine can induce positive, negative and cognitive schizophrenic-like symptoms in healthy subjects [1,115,139]. In addition, ketamine can precipitate and exacerbate symptoms in schizophrenic patients that are remarkably similar to specific hallucinations and delusions experienced in active phases of the patients’ illness [118,119,141]. These findings provide convincing support for the hypothesis that the pathophysiology of schizophrenia involves NMDA receptor function hypofunction.

Although PCP and ketamine have a number of neuropharmacological actions, their ability to block NMDA receptor function most likely accounts for their psychotomimetic effects [102]. For example, ketamine is 10× more potent at NMDA receptors than at the sigma receptor [165], and 5× more potent at the NMDA receptor than at the mu opiate receptor [184]. It is also a weak inhibitor of monoamine transporters [183] and weakly inhibits acetylcholinesterase [40]. However, drugs acting at those sites do not produce behavioral effects characteristic of ketamine. Thus, at the subanesthetic doses of ketamine required to induce schizophrenic-like symptoms, the molecular pharmacological profile of the drug suggests that NMDA receptor antagonism will predominate.

5.2. Developmental sensitivity to psychotomimetic effects of ketamine

The developmental concordance in sensitivity to psychotomimetic effects of ketamine and the onset of schizophrenia provides further support for the hypothesis that schizophrenia may involve NMDA receptor hypofunction. The psychotomimetic effects of NMDA antagonists are minimal or absent in children but become apparent in late adolescence and early adulthood [171,216] the time when schizophrenic symptoms typically first present. Also, preclinical studies have demonstrated a similar developmental sensitivity to the neurotoxic effects of NMDA antagonists [72]. The specific neurochemical mechanisms that mature in late adolescence and early adulthood and are responsible for ketamine-induced psychotomimetic effects are unknown. Defining the neurochemical substrates that underlay the developmental sensitivity to psychotomimetic effects of ketamine could provide critical insight into the pathophysiological basis of schizophrenia.

5.3. Effects of positive allosteric modulators of the NMDA receptor in schizophrenics

The therapeutic effects of positive allosteric modulators acting at the glycine regulatory site of the NMDA receptor support the NMDA hypofunction hypothesis of schizophrenia. Although inconsistent results have been reported by treating schizophrenic patients with glycine, administration of an appropriate dose of d-cycloserine, a partial agonist at the glycine regulatory site, improved negative symptoms of schizophrenia (reviewed by Goff and Wine [81]). The full glycine site agonist d-serine improved both negative and positive symptoms when added to standard antipsychotic drug treatment regimens [197]. Although the effectiveness of systemic treatments with the different glycine site modulators in enhancing NMDA receptor function is uncertain, the available clinical data with these compounds suggest that potentiating NMDA-mediated neurotransmission could represent a novel therapeutic strategy for treating schizophrenia.

6. Preclinical studies of NMDA receptor antagonists

6.1. Effects of ketamine on brain function

Although the ability of ketamine to antagonize NMDA receptors is well established [11,193,216] the effects of ketamine on brain function are poorly understood, especially in regard to psychotomimetic sub-anesthetic doses. Electrophysiological and metabolic mapping studies of the brain have demonstrated complex actions of ketamine on functional activity. Corssen and Domino [44] found that systemic administration of ketamine suppressed neuronal firing in the neocortex (isocortex) and thalamus but increased neural activity in the hippocampus. Other investigators observed increased activity in the thalamus and seizure responses in the amygdala and hippocampus after administration of ketamine [75,218]. Iontophoretic application of ketamine consistently reduced spontaneous and glutamate evoked unit activity in the hippocampus, amygdala, and ventral thalamic nucleus [182]. By contrast, i.p. administration of ketamine produced inconsistent responses and erratic firing patterns of neurons in these same brain regions [182]. Thus, at a cellular level after local application, ketamine appears to inhibit excitatory re-
Effects of ketamine on regional brain metabolism have been studied by measurement of $^{14}$C-deoxyglucose (2-DG) uptake. Anesthetic doses of ketamine increased uptake in the hippocampus and entorhinal cortex but decreased uptake in the medial geniculate, inferior colliculus, and in most isocortical regions [48,91,156]. Thus, as in the electrophysiologic studies, metabolic mapping investigations show that systemic administration of ketamine can produce both excitatory and inhibitory actions in the brain. In the early 2-DG studies with ketamine, the period of anesthesia did not last for the duration of the 2-DG uptake period. Consequently, for part of the survival time after injection of ketamine, the rats exhibited behavioral activation [48]. Therefore, some of the increased 2-DG uptake in certain brain regions may have been due to the actions of subanesthetic plasma levels of ketamine present during the elimination phase of the drug, while 2-DG was circulating.

As noted, subanesthetic doses of ketamine have been shown to produce psychotomimetic effects. Therefore, we examined the effects of subanesthetic doses of ketamine on regional 2-DG uptake, in order to identify potential neuroanatomical regions involved in ketamine-induced behavioral activation [65,66]. Subanesthetic doses of ketamine induced a characteristic behavioral response consisting of staggered locomotion and repetitive side-to-side head rocking [65,66]. The subanesthetic doses of ketamine increased 2-DG uptake substantially in certain limbic cortical regions, including medial prefrontal, ventrolateral orbital, cingulate, and retrosplenial cortices. In the hippocampal formation, ketamine induced prominent increases in 2-DG uptake in the dentate gyrus, stratum lacunosum-molecular, and presubiculum. Increased 2-DG uptake in response to ketamine was also observed in select thalamic nuclei and the basolateral nucleus of the amygdala. Similar patterns of brain metabolic activation were observed with the more selective NMDA antagonist MK-801 [64,117], suggesting that NMDA antagonistic properties of ketamine are responsible for its effects on 2-DG uptake.

In addition to the neuroanatomically selective functional activation indicated in the 2-DG studies, subanesthetic doses of ketamine also induced Fos-like immunoreactivity in selective limbic cortical regions, such as the medial prefrontal, ventrolateral, cingulate and retrosplenial cortices [66]. Consistent with these preclinical findings are data in humans showing that subanesthetic doses of ketamine may provide clues for the neuroanatomical basis of ketamine-induced exacerbation of schizophrenic symptoms.

6.2. Potential mechanisms for functional activation induced by NMDA antagonists

The functional activation induced by ketamine and other NMDA antagonists could result from antagonism of inhibitory neural mechanisms, such as blocking NMDA receptors on GABA-containing neurons. Indeed, benzodiazepines, which potentiate GABA-mediated inhibition, antagonize the emergence reactions in patients recovering from ketamine anesthesia [38,41,67]. In addition, benzodiazepines block ketamine-induced Fos in the cingulate cortex and retrosplenial cortex [155], and antagonize NMDA antagonist-induced cell damage in the retrosplenial cortex [162]. However, the effects of ketamine on cognition are not blocked by benzodiazepines, and in fact, ketamine-induced thought disorder may be worsened by lorazepam [116]. These data suggest that components of ketamine’s behavioral effects may be due in part, but not wholly, to disinhibitory effects involving GABA-containing neurons.

The mechanism for the excitatory action of ketamine on 2-DG uptake could also relate to the action of ketamine to increase brain extracellular fluid levels of glutamate and aspartate [31,149]. These excitatory amino acids could then activate non-NMDA receptors, including AMPA and kainate receptors [149]. In contrast to the increase in glutamate release by sub-anesthetic doses of ketamine, anesthetic doses of the drug decreased glutamate levels [149]. The effect of different doses of ketamine on excitatory amino acid levels are consistent with our observations of increased 2-DG uptake in response to a subanesthetic dose, and reduction in 2-DG uptake in response to an anesthetic dose of ketamine [66].

In support of the hypothesis that ketamine-induced behavioral effects relate to glutamate release, with consequent activation of AMPA receptors, administration of an AMPA antagonist partially reversed memory deficits induced by subanesthetic doses of ketamine in rats [149]. Additional data suggesting that excessive glutamatergic activity is involved in effects of NMDA antagonists are findings that AMPA/kainate receptor antagonists reduce NMDA antagonist-induced hyperlocomotion [29,92,217] and neurodegeneration [181]. Furthermore, PCP-induced behavioral effects and increased extracellular fluid levels of glutamate were antagonized by a Group II metabotropic agonist [150]. The authors suggest that these effects resulted from attenuating glutamate release via presynaptic autoreceptor stimulation.

6.3. Effects of antipsychotic drug treatment on responses to NMDA antagonists

In accord with the hypothesis that reduced NMDA receptor function may occur in schizophrenia are findings...
in rats that antipsychotic drugs can block certain effects of NMDA receptor antagonists. Both typical and atypical antipsychotic drugs have been shown to reduce neurotoxic effects of MK-801 [70,71] and antagonize MK-801-induced behavioral activation [43,93,194]. However, certain behaviors are differentially affected by typical and atypical antipsychotics. For example, clozapine and olanzapine antagonized PCP-induced social withdrawal, but raclopride and haloperidol did not affect this drug-induced behavior [43]. Clozapine was also able to reduce behavioral deficits induced by chronic PCP treatment in monkeys [105]. Also, drugs with atypical antipsychotic properties, but not typical antipsychotics, reduced NMDA antagonists-induced deficits in prepulse inhibition [15,16,191].

Strikingly differential effects of clozapine and haloperidol have also been observed on NMDA antagonist-induced brain metabolic activation and electrophysiological effects. Clozapine completely blocked the effects of ketamine on 2-DG uptake, whereas a cataleptic dose of haloperidol did not block, but instead potentiated the effects of ketamine [65]. In electrophysiological investigations, the selective 5HT2A antagonists MDL100907 and clozapine prevented PCP-induced blockade of NMDA responses, but haloperidol did not produce a similar effect [209]. Similarly, clozapine, but not haloperidol, potentiated electrophysiological activation in the prefrontal cortex after stimulation of the corpus callosum [13]. Thus in a variety of experimental settings, differential effects of typical and atypical antipsychotic drugs are observed on functional alteration induced by NMDA antagonists. The ability of atypical, but not typical antipsychotics, to attenuate NMDA antagonist-induced alterations in behavioral responses, 2-DG uptake and electrophysiological activity suggests that the therapeutic effects of atypical antipsychotic drugs could be related to counteracting NMDA receptor hypofunction.

Although limited data exist from human studies, the available information suggests differential effects of typical and atypical antipsychotic drugs on behavioral responses to ketamine. Patients treated with haloperidol did not exhibit reduced psychotic responses to a challenge dose of ketamine [119]. By contrast, schizophrenia patients treated with clozapine exhibited reduced thought disturbance in response to the NMDA antagonist [140]. These data parallel the preclinical studies indicating that atypical antipsychotics, but not typical antipsychotics, block effects of NMDA antagonists.

7. Potential links between dopamine and NMDA hypotheses of schizophrenia

There are well-documented interactions between NMDA and dopamine systems that may provide a framework to unify the dopamine and NMDA hypotheses of schizophrenia. Treatments that interfere with dopamine function reduce NMDA antagonist-induced behavioral activation [47,79,93,137,163,164] and cognitive deficits [202]. Although MK-801 is capable of producing behavioral activation in monoamine-depleted mice [34], when compared to intact animals, the behavioral response is distinctly different and higher doses are required to induce behavioral changes [33,130]. Thus, NMDA antagonists may induce behavioral effects independent of dopamine, but under normal conditions, dopamine neurotransmission contributes to the behavioral effects of these drugs [29].

Additional support for important interactions between NMDA and dopamine systems is that dopamine turnover and release is selectively activated in the nucleus accumbens and medial prefrontal cortex of rats after systemic administration of NMDA antagonists [27,29,94,98,109,176,202,211,221]. Although robust increases of dopamine release in the mesolimbic and mesocortical projection systems are consistently reported after administration of NMDA antagonists, little or no change in release of the catecholamine is found in the caudate–putamen in the same rats. However, in humans, PET studies of dopamine receptor occupancy after administration of ketamine suggest that the NMDA antagonists increase dopamine release in the striatum [24,185].

In accord with the in vivo microdialysis and PET studies of dopamine release, NMDA receptor antagonists increase the firing rate of midbrain dopamine neurons when administered systemically [77–80,151,176,188]. As noted, microdialysis studies indicate NMDA antagonists in rats selectively stimulate DA release from mesolimbic and mesocortical projection cells (A10, ventral tegmental area). By contrast, electrophysiological studies uniformly find that NMDA antagonists increase activity in both A10 and A9 (substantia nigra) neurons. The discrepancy between the electrophysiological and microdialysis studies with regard to the neuroanatomical specificity of NMDA antagonists may be due to the anesthesia used in electrophysiological investigations [176].

Although acute administration of NMDA receptor antagonists increases dopamine turnover and release, subchronic administration of PCP (7–14 days) has been demonstrated to reduce dopamine in the prefrontal cortex [103,105]. In monkeys, this effect of subchronic PCP treatment is selective for the dorsolateral prefrontal cortex and prelimbic cortex and has been suggested to contribute to cognitive deficits induced by the NMDA antagonists [103]. These data suggest that protracted NMDA receptor hypofunction can produce alterations in prefrontal dopaminergic activity postulated to occur in schizophrenia [55,214].

8. NMDA receptors and sensitization of dopamine systems

There is substantial data showing that NMDA antagonists can prevent the development of stimulant induced
behavioral sensitization in certain experimental paradigms (for review see Ref. [220]). However, the generalized conclusion that reduced NMDA receptor function blocks the development of dopaminergic sensitization has been questioned, based on recent data demonstrating that NMDA receptor antagonists can either enhance or interfere with stimulant-induced sensitization, depending on the specific experimental situations (for review see Ref. [201]). For example, MK-801 suppressed sensitization of amphetamine-induced stereotopic behaviors, but potentiated locomotor sensitization to the stimulant [180]. Also, locomotor sensitization induced by the D2/D3 agonist bromocriptine was enhanced by MK-801 [219]. Furthermore, MK-801 potentiated the development of stress-induced sensitization to the locomotor effects of amphetamine [195] and chronic PCP administration potentiated stress- and amphetamine-induced hyperlocomotion [104]. In relation to the NMDA hypofunction hypothesis of schizophrenia, these data suggest that reduced NMDA receptor function could facilitate sensitization of the dopamine systems.

9. Stress vulnerability and schizophrenia

The onset of schizophrenia is frequently precipitated by a stressful event and psychological stress is well documented to precipitate or exacerbate psychotic symptoms [27,56,142,144,157]. Stress-reduction strategies have significant impact on reducing relapse rates in schizophrenic patients [121]. Such observations suggest that schizophrenia develops when a threshold of stress tolerance is exceeded in a vulnerable individual [7,212]. Moreover, some schizophrenia patients are susceptible to relapse due to psychological stressors, even while maintained on antipsychotic medication [108]. Stimulant abusers, similarly, have a propensity to experience a psychotic relapse in the context of psychological stress, even during periods of abstinence [175].

Preclinical studies have demonstrated that stress stimulates dopamine release preferentially in the mesolimbic projection system (for review see Ref. [173]). Stress also increases glutamate release preferentially in the medial prefrontal cortex [148]. In metabolic mapping work, stress was shown to increase 2-DG uptake [61,63] and Fos induction [17,53,62,63] in the medial prefrontal cortex and nucleus accumbens. Interestingly, rats sensitized by chronic amphetamine show increased behavioral response to stress and exhibit greater increases in dopamine release in the medial prefrontal cortex in comparison to control rats [90]. Conversely, chronic stress can increase behavioral responses to dopaminergic stimulants [12,107,195]. The ability of MK-801 to enhance the stress-induced sensitization to amphetamine [195] is provocative in relation to the NMDA receptor hypofunction hypothesis of schizophrenia.

10. An integrated pathophysiological model of schizophrenia

Schizophrenia may be the result of a sequence of events (failures in neural development, migration and connectivity) that begins with a congenital or early developmental deficiency. As a result of this deficiency, patients with schizophrenia may be more susceptible to the neurophysiological perturbations of environmental experiences that occur in the context of daily life, as their compensatory capacity is compromised and more easily breached. If prolonged or recurrent, such perturbations can lead to a persistent state of dysregulation, and potentially enduring pathologic changes, which are at first functional and ultimately structural. This longitudinal process is proposed to occur in three related but distinct stages with different temporal, pathophysiological and clinical characteristics [129].

The postulated first stage is caused by genetic and/or epigenetic etiologic factors (as previously described) that occur during gestation and early perinatal development. Such factors could involve the failure of normal neuronal development, migration and synaptogenesis. The result may be a deficiency in the regulatory capacity of the cortex on subcortical structures. The cellular basis for this deficiency may be reflected in the histopathologic, cytoarchitectural [2,4,19,20,22,113,170,173] and morphometric [6,23,87] abnormalities described in the prefrontal and temporal cerebral cortical regions of schizophrenia patients. Support for this conceptualization is evidenced by altered functional activity in the prefrontal cortex of schizophrenic patients [8,87,181,214] and chronic cocaine users [203]. This neuropathology may clinically manifest as some of the cognitive, social and motor deficits that are behavioral precursors to schizophrenia [60,76,207,210].

A deficiency in neuronal modulatory capacity could lead to the second pathophysiological stage that occurs in adolescence and early adulthood. During this period, stressful, but normative human experiences, (e.g., family strife, going to college, entering military service) stimulate perturbations in neuronal activity that could otherwise be endured without psychopathological consequences. However, with diminished regulatory capacity, progressive neurochemical sensitization may occur. A possible reason that the modulatory deficiency does not produce sensitization earlier (in childhood and early adolescence, though in some patients this does occur) may be due to the redundancy in neural synaptic connections that exists through adolescence, which temporarily compensates for the deficiency. The deficiency only becomes apparent when, in late adolescence or early adulthood, redundant synaptic connections are eliminated through neural pruning and the circuits refined to the point that the threshold of modulatory capacity is exceeded [74,96]. In this regard, the emergence of sensitivity to psychotomimetic effects of ketamine in late adolescence and early adulthood [171,216]...
implicates altered NMDA receptor function in this reduced regulatory capacity.

Another factor that may contribute to the delay in the onset of psychosis in schizophrenia is the need for repetition and intermittency of neurochemical stimulation in response to environmental events, potentially leading to a pathological sensitization. Grace [82,83] has suggested that, in schizophrenia, phasic (as opposed to tonic) DA release may be a neurophysiologic correlate to the intermittent pharmacologic stimulation critical for induction of behavioral sensitization by DA agonists in rodents. Phasic DA release is dependent on VTA DA neuronal depolarization and impulse activity, and can result in an irregular burst firing pattern of large amplitude and transient increases in DA release [85]. Moreover, indirect DA agonists, such as amphetamine and cocaine, potentiate impulse dependent DA release [205] while antipsychotic medications, which appear to interrupt the sensitization process in schizophrenia [135,223], may exert their therapeutic effects by depolarization-induced inactivation of DA cell firing [30,215]. Since NMDA antagonists activate dopaminergic neurons [77–80,151,176,188], reduced NMDA receptor function could be a predisposing factor for the diminished regulatory capacity of these cells.

Dysregulation of inhibitory feedback mechanisms involved in the regulation of VTA neuronal activity may result in a pathological potentiation of impulse-dependent phasic DA release [82,84]. This pathological state could represent a new equilibrium between phasic and tonic DA release mechanisms [84]. Accordingly, when VTA neurons are again stimulated (by normative, stressful or pharmacologic stimuli) the phasic DA release is excessive in the absence of normal inhibitory control mechanisms. In schizophrenia a condition of behavioral sensitization may exist, which is postulated to be associated with an increase in DA activity in the nucleus accumbens, and interestingly, a decrease in extracellular DA in the prefrontal cortex [55,214]. These hypothesized regionally distinct effects on dopamine release are consistent with preclinical data indicating a reciprocal relationship can exist for DA release in the accumbens and prefrontal cortex [104,106,169,187]. A deficiency in corticostriatal glutamatergic innervation has been postulated to occur in schizophrenia [19,32,45,82,102,161,198] and could represent a neurochemical correlate to a preexisting compromise that would facilitate sensitization of dopamine systems. Thus it is possible that prefrontal and temporal cortical pathology could facilitate the development of behavioral sensitization, as it would appear to augment the mesolimbic response to stress and also possibly to psychoticogenic drugs (e.g., stimulants, PCP, ketamine). Weinberger et al. have reported evidence consistent with this. Chemical deafferentation of the prefrontal cortex by excitotoxin injection produced no significant alteration in basal DA levels or turnover in the basal ganglia or in DA-related behaviors. However, markedly elevated DA mesolimbic activity was observed when the lesioned animals were exposed to stressful stimuli [101]. Similar results have been found after surgical ablation of the prefrontal cortex. [133]. In addition, neonatal lesions of the ventral hippocampus result in enhanced sensitivity to behavioral effects of dopamine agonists in postpuberal (but not prepuberal) rats [131–134,222]. These data are consistent with the proposed deficiency in corticostriatal glutamatergic innervation in schizophrenia.

The hypothesized sensitization process in schizophrenia could involve maladaptive responses to stress. Stressors of mild intensity or duration selectively activate VTA neurons and increase DA release in the prefrontal cortex, while more intense stressors also increase dopamine metabolism and release in the nucleus accumbens [173]. Prefrontal cortical efferents (presumably glutaminergic) can regulate DA release in subcortical structures and are involved in stress-induced DA release [57,82,169]. These data, together with the findings that repeated treatment with NMDA antagonists can result in enhanced responses to stress and amphetamine challenge [104,195] suggest that altered NMDA–DA interactions could contribute to maladaptive responses to stress.

In the foregoing conceptualization of stages 1 and 2, an endogenous dopaminergic sensitization process may occur in schizophrenia, perhaps secondary to a developmental pathology involving NMDA receptor hypofunction. A third stage in the pathophysiology of schizophrenia underlies the deteriorative and residual phases of the illness, and involves the development of structural neuronal changes, which are consequential to prolonged sensitization. The existence of this stage is controversial, but is consistent with the persistent and irreversible nature of the morbidity in some patients.

11. Conclusions

The clinical course of schizophrenia suggests that the disease unfolds in distinct phases. Initially, there is a developmental insult to the CNS that does not result in psychosis (stage 1), but may underlie the subtle cognitive, motor and social impairments exhibited premorbidly. This developmental insult may involve reduced NMDA receptor function, which could in turn facilitate sensitization in dopamine systems (stage 2) leading to the formal onset of the illness. If persistent or recurrent, such endogenous (perhaps stress-related) sensitization could progress to a self-limiting degenerative phase (stage 3) manifested by persistent morbidity, treatment resistance and clinical deterioration. This conceptual model attempts to account for the clinical phenomena of the illness and its longitudinal course, as well as the enhanced sensitivity to stress, psychostimulants, and NMDA antagonists observed in patients with schizophrenia. Although clearly speculative, the model is supported by existing evidence and provides direction for future experimental investigations.
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