New approaches to the management of schizophrenia: focus on aberrant hippocampal drive of dopamine pathways

Stephanie M Perez
Daniel J Lodge
Department of Pharmacology and Center for Biomedical Neuroscience, University of Texas Health Science Center, San Antonio, TX, USA

Abstract: Schizophrenia is a disease affecting up to 1% of the population. Current therapies are based on the efficacy of chlorpromazine, discovered over 50 years ago. These drugs block dopamine D2-like receptors and are effective at primarily treating positive symptoms in a subset of patients. Unfortunately, current therapies are far from adequate, and novel treatments require a better understanding of disease pathophysiology. Here we review the dopamine, gamma-aminobutyric acid (GABA), and glutamate hypotheses of schizophrenia and describe a pathway whereby a loss of inhibitory signaling in ventral regions of the hippocampus actually drives a dopamine hyperfunction. Moreover, we discuss novel therapeutic approaches aimed at attenuating ventral hippocampal activity in a preclinical model of schizophrenia, namely the MAM GD17 rat. Specifically, pharmacological (allosteric modulators of the GABA<sub>α</sub> receptor), neurosurgical (deep brain stimulation), and cell-based (GABAergic precursor transplants) therapies are discussed. By better understanding the underlying circuit level dysfunctions in schizophrenia, novel treatments can be advanced that may provide better efficacy and a superior side effect profile to conventional antipsychotic medications.

Keywords: dopamine, GABA, glutamate, schizophrenia, hippocampus, MAM rat

Introduction
Schizophrenia is a severe psychiatric disorder for which there is currently no cure. Affecting approximately 1% of the population,<sup>1,2</sup> schizophrenia is believed to be a developmental disorder with symptoms typically appearing during adolescence and early adulthood.<sup>3</sup> There are three major symptom clusters associated with this disease: positive (psychosis, disorganized thinking and speech, hallucinations, delusions), negative (anhedonia, social withdrawal), and cognitive deficits (reversal learning, working memory deficits).<sup>4,5</sup> Common pharmacological interventions for the treatment of schizophrenia include typical and atypical antipsychotic drugs which primarily act to decrease positive symptoms by the blockade of D2-type dopamine receptors.<sup>6,7</sup> Unfortunately, antipsychotic drugs are not always effective at reducing positive symptoms,<sup>8,9</sup> are largely ineffective at treating negative and cognitive deficits,<sup>10–13</sup> and are associated with debilitating adverse side effects such as movement<sup>4</sup> and metabolic disorders.<sup>4</sup> For these reasons, the rates of discontinuance are relatively high<sup>4</sup> and novel therapeutic approaches are required to better treat this devastating neuropsychiatric disease. Here we review some basic theories of schizophrenia and attempt to provide an integrated hypothesis that combines gamma-aminobutyric acid (GABA)ergic, glutamatergic, and dopaminergic theories to provide a framework by
which therapeutic approaches targeting the hippocampus as a novel region can be established for the treatment of schizophrenia.

Antipsychotic drugs

While there are numerous adjunct therapies, antipsychotic drugs have been the first line of treatment for schizophrenia since the advent of chlorpromazine in the 1950s. Chlorpromazine largely replaced surgical and electroconvulsive approaches for the treatment of psychiatric symptoms and has been heralded as one of the most significant advances in the field of psychiatry. Since this time, there has been extensive research into the mechanisms underlying the effects of antipsychotic medications. It has been established that all antipsychotic drugs are dopamine D2-like receptor antagonists and produce effects by blocking dopamine receptors. The typical, or first generation, antipsychotic drugs are effective at reducing positive symptoms, likely attributable to their ability to block dopamine receptors in the mesolimbic dopamine system. Unfortunately, they also cause dopamine receptor blockade in the nigrostriatal, mesocortical, and tuberoinfundibular dopamine systems, which is associated with a number of debilitating extrapyramidal side effects including Parkinson’s-like symptoms (tremors, muscle rigidity, tardive dyskinesia) and hyperprolactinemia.

Atypical or second-generation antipsychotics were approved by the FDA in the late 1980s, as they were believed to be more effective at treating symptoms of schizophrenia without the motor side effects. Much like typical antipsychotics, atypical antipsychotics bind to dopamine receptors; however, atypical antipsychotics also display an affinity for the serotonin-2A (5HT-2A) receptor. Indeed, the ratio of 5HT-2A to dopamine D2 receptor affinity distinguishes typical and atypical antipsychotic drugs better than any known pharmacological feature. Given that 5HT-2A receptors are located presynaptically on dopamine terminals in the nigrostriatal and mesocortical pathways, atypical antipsychotics augment dopamine release in these regions to counteract the effects of D2 antagonism. The net result is that atypical antipsychotics maintain efficacy against positive symptoms by transiently occupying D2 receptors and rapidly dissociating to allow for normal dopamine neurotransmission, while providing fewer extrapyramidal side effects. Additionally, 5HT-2A receptors are not only localized on dopamine terminals but are widely expressed throughout the cortex, where these receptors also contribute to the beneficial effects of atypical antipsychotics. Indeed, patients who take atypical antipsychotics also report mild improvements in cognition and reductions in suicidal thoughts and negative symptoms, which are not commonly observed with typical antipsychotics. It should be noted that while atypical antipsychotics produce fewer motor side effects associated with blockade of dopamine receptors, they cause severe metabolic side effects, including weight gain and glucose intolerance.

To evaluate the effectiveness of various antipsychotic drug treatments, a number of large trials have been undertaken, including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS) and the European First-Episode Schizophrenia Trial (EUFEST). These studies, and others, have demonstrated that there are no dramatic differences in the efficacies of typical and atypical antipsychotic treatments. However, a striking observation was that the vast majority of patients (~74%), independent of the type of antipsychotic treatment, discontinued their treatment during Phase I due to ineffectiveness or intolerable side effects, clearly demonstrating that current therapeutic approaches are far from adequate. For these reasons, it is essential to identify novel therapeutic approaches for the treatment of schizophrenia. To do this, one must start with a more complete understanding of the pathophysiology of schizophrenia.

The dopamine hypothesis

The dopamine hypothesis of schizophrenia is one of the more predominant theories advanced to explain symptoms of the disease. It posits that hyperactivity of mesolimbic dopamine transmission underlies positive symptoms of schizophrenia. Observations that validate this hypothesis include the finding described above that all antipsychotic drugs bind to and block dopamine D2 receptors. In addition, indirect dopamine agonists, such as amphetamine, have been demonstrated to induce psychosis in the general population, whereas individuals with schizophrenia are significantly more sensitive to the dopamine-releasing effects of amphetamine. Additional evidence for the dopamine hypothesis stems from human imaging studies providing evidence for region-specific increases in dopamine transmission in individuals with schizophrenia, particularly in the associative areas of the striatum. Specifically, positron emission topography (PET) studies demonstrate a higher occupancy of striatal dopamine D2 receptors by dopamine in individuals with schizophrenia, predictive of antipsychotic effectiveness, whereas 18F-DOPA PET studies have demonstrated an elevated dopamine synthesis capacity in striatal regions. It should be noted that while studies examining...
D2 receptor availability are not entirely consistent, changes in presynaptic dopamine function are more reliable with a recent meta-analysis demonstrating an effect size of $d=0.8$.48

An association between aberrant dopamine neurotransmission is not only correlated with positive symptoms of the disease, but has also been suggestive to be a contributing factor to cognitive deficits observed in patients.47,49 In contrast to that observed in the mesolimbic system, a decrease in dopamine transmission to the cortex may underlie deficits in working memory and executive function.50 Specifically, dopamine transmission in the dorsal lateral prefrontal cortex produces an inverted U-shaped dose response curve whereby both decreases and increases in dopamine signaling can impair working memory and executive function.51 Taken together, there is considerable evidence for aberrant dopamine signaling in individuals with schizophrenia that likely contributes to both positive and cognitive symptoms.38 However, it is important to note that there appears to be a lack of an overt pathology within the midbrain dopamine system.52 This has led to the suggestion that it is the regulation of dopamine neuron transmission that is dysfunctional in schizophrenia.53

The glutamate and GABA hypotheses

While considerable evidence indicates a dysregulation of dopamine signaling in schizophrenia, this is likely secondary to aberrant regulation by glutamatergic and GABAergic systems. The glutamate hypothesis of schizophrenia centers on hypofunctionality of glutamate signaling via N-methyl-D-aspartate (NMDA) receptors. Thus, NMDA receptor antagonists, such as phencyclidine (PCP) and ketamine, produce both psychotomimetic effects as well as cognitive impairments in humans.54,55 For this reason, considerable preclinical work has been performed following either acute or subchronic administration of NMDA receptor antagonists.56-59 Drugs like PCP inhibit signaling by the NMDA receptor and produce behavioral deficits in rodents that are analogous to positive (hyperlocomotion) and negative (social interaction deficits) symptoms as well as cognitive deficits (deficits in reversal learning and extradimensional set shifting), which coincide with what is seen in the clinic. Additionally, perinatal PCP treatments have been used to model altered brain pathologies commonly observed in individuals with schizophrenia, such as altered expression of NMDA receptors and parvalbumin-containing interneurons.60 More recently, genetic studies have demonstrated the potential involvement of aberrant glutamatergic signaling in schizophrenia. Specifically, a transgenic mouse model with reduced NMDA receptor expression displays behaviors related to schizophrenia, such as increased locomotor activity and decreased social interaction, both of which were reversed by administration of the antipsychotic clozapine.66 Interestingly, it appears that the net effect of NMDA receptor antagonism is to augment glutamatergic transmission. While at first glance this may seem counterintuitive, it is thought that NMDA receptor antagonists preferentially alter GABAergic activity due to the more depolarized membrane potential and subsequent lack of Mg$^{2+}$ block of the NMDA receptor.67,68 This would lead to increases in glutamatergic signaling. Indeed, magnetic resonance spectroscopy studies have demonstrated increased levels of glutamine in first-episode, untreated schizophrenia patients that provides in vivo evidence for enhanced glutamatergic activity.69

Deficits in GABAergic neurotransmission have been consistently demonstrated in post mortem studies of individuals with schizophrenia.70 These studies have shown alterations in GABAergic markers, including glutamic acid decarboxylase, parvalbumin (PV), somatostatin, and calretinin, to name a few.71-75 Various subtypes of interneurons exist that provide inhibitory control and modulation of cortical and hippocampal circuits.71 These interneuron subpopulations can be reliably distinguished by the neurochemicals they express. The cortex and hippocampus both contain interneurons that differentially express calcium binding proteins (PV, calretinin, calbindin) and neuropeptides (somatostatin, neuropeptide Y) with distinct cell types playing a vital role in inhibitory control over pyramidal cell activity in both regions.71,76-78 This is important, as it appears that the GABAergic dysfunction in schizophrenia is restricted to subpopulations of interneurons; ie, those containing PV or somatostatin.78-80 PV containing interneurons are fast firing, perisomatic targeting, and are thus situated to regulate pyramidal cell firing.71,75,81 In addition, these cells contribute to large scale neuronal oscillations within and between brain regions that are thought to be essential for cognitive function, and are known to be altered in individuals with schizophrenia.75,82,83

Information from genetics studies

Arguably, the most widely replicated biological factor in regard to schizophrenia is a family history of the disease.84 Over the years, researchers have studied the families of patients diagnosed with schizophrenia, along with fraternal and identical twin studies, in order to determine whether genetics plays a role in the disease. A quantitative meta-analysis of published twin studies of schizophrenia
was conducted, and found that the heritability of the disease is very high (point estimate, 81%), consistent with prior summaries of literature on twins. It is important to note that no single gene has been identified as being solely responsible for the development of schizophrenia; rather, there are several candidate genes associated with an increased risk for the disease (ie, disrupted in schizophrenia 1,90–92 and neuregulin 1193,94). Thus, genome-wide association studies (GWAS) have been instrumental in identifying candidate genes that may play a role in the heritability of schizophrenia. Specifically, GWAS examine the entire genome to detect common genetic variants in different individuals in order to implicate specific variants in disease risk. Because schizophrenia is a heterogeneous disease, rare variants with large effects have a very low frequency in the population as a whole, and are consequently not detectable by population-based GWAS. However, of relevance to the hypotheses detailed above, there have been reports implicating abnormalities in GABAergic and glutamatergic systems, as well as candidate genes involved in neurodevelopment (ie, EFHD1, RELN, ANK3, NRG1, etc). It should be noted, however, that individual results from GWAS have not identified overlapping polymorphisms nor do candidate genes consistently reach the level of genome-wide statistical significance, leaving many unanswered questions about the genetics of schizophrenia. This is not surprising, as it is commonly accepted that schizophrenia is associated with many genes that contribute modestly to the risk of developing the disease. However, when a combination of genetic alterations is placed in the context of environmental factors, they contribute to the pathophysiology of the disorder.

Towards an integrated hypothesis

Post mortem studies have identified structural alterations in human patients that are largely associated with cortical and hippocampal regions. These regions are also those that display consistent decreases in the expression of the interneuron marker PV as well as deficits in activation during task performance, as measured by functional imaging studies. It is not currently understood how alterations within these specific neuronal systems contribute to the symptoms associated with schizophrenia. Thus, preclinical research is required that utilizes animal models that closely recapitulate several facets of the disease state. Animal models of schizophrenia can be generalized into three main categories: pharmacological, developmental, and genetic. The model which we typically utilize is a developmental disruption model that involves the administration of the mitotoxin methylazoxymethanol acetate (MAM) to pregnant dams on gestational Day 17. The offspring of these dams display anatomical, neurophysiological, and behavioral alterations consistent with those observed in individuals with schizophrenia. The exact mechanism as to how MAM produces a schizophrenia-like phenotype in rodents is not clear; however, this short-acting deoxyribonucleic acid (DNA)-alkylating agent is thought to alter cell division and gene expression (via DNA methylation).

Given the significant evidence for mesolimbic dopamine hyperfunction in schizophrenia (see above), we have examined the regulation of dopamine neuron activity in the MAM model of schizophrenia. Using in vivo extracellular recordings from dopamine neurons in the ventral tegmental area (VTA), it has been previously demonstrated that distinct brain regions can differentially modulate discrete dopamine neuron activity states. Of relevance to schizophrenia are the ventral subfields of the hippocampus (vHipp) and the medial prefrontal cortex. Activation of the vHipp has been demonstrated to increase dopamine levels in the forebrain by increasing the number of spontaneously active dopamine neurons in the VTA (defined as population activity). In contrast, activation of the medial prefrontal cortex produces more selective alterations in dopamine neuron firing rate and pattern. Electrophysiological recordings in the MAM model of schizophrenia have demonstrated a pathological increase in dopamine neuron population activity without alterations in firing rate or pattern, thus implicating the vHipp. It is thought that alterations in dopamine neuron population activity provide a gain of function whereby phasic stimuli can be amplified or attenuated by hippocampal inputs in response to environmental context or novelty. A pathological increase in dopamine neuron population activity would therefore lead to an abnormally high salience being ascribed to previously innocuous stimuli and may contribute to the delusions and paranoia exhibited by individuals with schizophrenia. Indeed, recent evidence from human imaging studies supports the notion that aberrant hippocampal activity may underlie the dopamine dysregulation observed in individuals with schizophrenia. Specifically, elevated baseline activity is present in the anterior hippocampus of patients and in the analogous vHipp of rodent models. To demonstrate the involvement of the vHipp in this pathologically enhanced dopamine neuron activity in a rodent model, the vHipp was pharmacologically inactivated by the administration of the Na+-channel blocker, tetrodotoxin. While having no significant effect in control animals, tetrodotoxin inactivation of the vHipp completely
reversed the elevated dopamine neuron population activity in MAM-treated rats.\textsuperscript{110} It is important to note that the effects of MAM on rodents are global and not simply restricted to the hippocampus. Therefore, it is likely that MAM produces alterations in afferents to the VTA and/or nucleus accumbens that also modulate dopamine activity and release in a freely behaving animal. Moreover, at face value, the hypothesis of hyperactivity within hippocampal subfields may appear inconsistent with one of the most well-known rodent models of schizophrenia, the neonatal ventral hippocampal lesion model.\textsuperscript{120} However, on the basis of work by Swerdlow et al, it has been suggested that behavioral abnormalities in the neonatal ventral hippocampal lesion model reflect, at least in part, aberrant function within spared elements of the hippocampal complex.\textsuperscript{121} Specifically, rats with large lesions encompassing the entire vHipp do not display the augmented responses to psychomotor stimulants consistently observed in rodent models and individuals with schizophrenia.\textsuperscript{121} These data suggest that the hypothesis of aberrant vHipp drive of the dopamine system may not be specific to the MAM model and may actually reflect a common pathophysiology in a number of diverse rodent models. Indeed, we have also demonstrated a similar observation in the subchronic phencyclidine rodent model (unpublished observations).

As mentioned above, evidence from postmortem studies suggests a decrease in PV interneuron function in individuals with schizophrenia.\textsuperscript{70,122} Given that these interneurons are well situated to regulate pyramidal cell activity,\textsuperscript{70} we posit that a decrease in PV interneuron function may actually underlie the hippocampal hyperactivity, and consequent dopamine neuron hyperfunction in schizophrenia. Indeed, a loss of PV function induced by degrading the extracellular matrix support structure of the PV interneurons was sufficient to increase hippocampal pyramidal neuron activity and produce enduring changes in dopamine system function.\textsuperscript{123} Similar results have been obtained by hippocampal selective knockdown of PV itself (unpublished observations). Taken together, we suggest that schizophrenia may be associated, at least in part, with a loss of interneuron control over hippocampal activity. This results in a pathologically enhanced hippocampal drive of the dopamine system that is likely associated with the positive symptoms of the disease (see Figure 1).

The hippocampus as a potential therapeutic target

Given that a deficit in hippocampal GABAergic transmission may contribute to the pathophysiology of schizophrenia, it stands to reason that targeting this system may provide a novel approach for the treatment of schizophrenia. Indeed, we have evidence that pharmacological,\textsuperscript{124,125} neurosurgical,\textsuperscript{112} and cell-based therapies\textsuperscript{115} are effective in reversing aberrant neuron activity and behaviors in the MAM rodent model of schizophrenia.

There is considerable preclinical and clinical data demonstrating a robust augmentation of GABAergic transmission by allosteric modulators of the GABA\textsubscript{A} receptor.
Indeed, the benzodiazepine and barbiturate classes of drug are widely utilized in this regard. Benzodiazepines have also been prescribed alone and in conjunction with antipsychotic medication for the treatment of schizophrenia, but the evidence as to its effectiveness as a treatment for schizophrenia is lacking and inconclusive to date, and may even be associated with an increased mortality. In addition, the extensive distribution of the GABA_A receptor makes it difficult to target specific brain regions with conventional medications. The GABA_A receptor is a pentameric structure consisting of a number of distinct subunits. Interestingly, the α5 subunit is preferentially expressed in the hippocampus, leading to the suggestion that positive allosteric modulation of α5 subunit containing GABA_A receptors may be effective in treating symptoms associated with schizophrenia. Indeed, the systemic administration of a selective allosteric modulator of the α5GABA_A receptor, SH-053-2’F-R-CH3, attenuated hippocampal activity in the MAM-model of schizophrenia. Furthermore, this was associated with a restoration of aberrant dopamine neuron activity, as well as reversing the behavioral hyperactivity to amphetamine. These data provide preclinical evidence that allosteric modulators of the α5GABA_A receptor may be an effective therapeutic approach to reverse dopamine hyperactivity by targeting aberrant hippocampal function.

In addition to the pharmacological targeting of hippocampal transmission, surgical approaches may also be effective at altering hippocampal activity. Deep brain stimulation (DBS), although still a very controversial treatment, has been gaining in popularity for the treatment of psychiatric disorders such as depression and obsessive compulsive disorder. It is thought that, in cortical regions, DBS acts to induce a functional lesion (likely by depolarization blockade of pyramidal neurons). For this reason, it was suggested that DBS of the vHipp may be a novel and effective therapeutic approach to treat the hippocampal hyperactivity thought to contribute to the symptoms of schizophrenia. Indeed, DBS of the anterior hippocampus has been demonstrated to be well tolerated in human patients (treated for epilepsy) with minimal side effects. We have recently demonstrated that vHipp DBS in MAM-treated rats is able to reverse aberrant dopamine neuron activity and the behavioral hyper-responsivity to psychomotor stimulants, thought to be an index of positive symptomatology. Given that current approaches are often ineffective at reducing cognitive symptoms, we examined the effect of vHipp DBS in a working memory task analogous to the Cambridge Neuropsychological Test Automated Battery in patients. MAM-treated rats demonstrated deficits in reversal learning and extradimensional set shifting, consistent with deficits observed in patients. Interestingly, vHipp DBS was able to ameliorate these deficits in the MAM rodent model. These studies suggest that hippocampal DBS may represent a novel therapeutic approach, not only for the dopamine-dependent symptoms but also for the cognitive deficits. It should be noted that this is based on our recent preclinical study in rodents and that DBS treatments in humans are still experimental; while the hippocampus has been targeted in epilepsy, underlying differences in pathology suggest that effects in schizophrenia may be variable.

As mentioned earlier, a central hypothesis is that a decrease in P5 expression underlies deficits in GABAergic signaling that contribute to the symptoms of the disease. Thus, restoring PV interneuron function would be expected to directly reverse the pathophysiology of the disorder. To test this hypothesis, we have used a cell-based therapy in an attempt to replace the deficient interneurons in the hippocampus. GABAergic precursor cells were obtained from the medial ganglionic eminence (MGE) and transplanted in the vHipp of MAM-treated rats. The transplanted cells were shown to display a GABAergic phenotype and migrate away from the site of injection to integrate within existing circuitry. In addition, MAM-treated rats transplanted with vHipp MGE neurons demonstrated a restoration of hippocampal function and consequent normalization of aberrant dopamine neuron activity. Finally, the increased sensitivity to amphetamine was also reversed following MGE transplants. Thus, interneuron transplants were effective in treating aberrant neurophysiology and behavior in the MAM model of schizophrenia and may provide the framework for a more permanent therapeutic approach for the treatment of schizophrenia.

**Summary**

For the last 50 years or so, the treatment of schizophrenia has relied on dopamine receptor antagonists that are not always effective and are often associated with debilitating side effects. For this reason, it is essential to develop novel therapeutic approaches. To do this, one must better understand the underlying pathophysiology of this disease. Here we report on an integrated hypothesis of schizophrenia that, while it may not be all encompassing, provides a potential novel site of intervention. Specifically, it is suggested that the aberrant dopamine system function, thought to underlie the positive symptoms of the disease, is secondary to hyperactivity within hippocampal subfields. Furthermore, this hyperactivity is likely attributable to a decrease in intrinsic GABAergic
signaling by PV interneurons within the hippocampus. Therefore, approaches aimed at restoring hippocampal function may provide a novel approach for the treatment of schizophrenia. Indeed, here we provide preclinical data demonstrating the effectiveness of three distinct experimental approaches (pharmacological, neurosurgical, and cell-based) in a rodent model of schizophrenia. Future experiments in additional rodent and primate models are warranted before such novel approaches are translated to the clinic.

Disclosure
The authors report no conflicts of interest in this work.

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