Minireview

Bringing Order to the Glutamate Chaos in Schizophrenia

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Recent genetic linkage studies complement the existing evidence that implicates abnormalities in NMDA receptor-mediated neurotransmission in the pathophysiology of schizophrenia. At the same time, advances in our understanding of the complex mechanisms that modulate the function of NMDA receptors suggest several novel sites for pharmacological manipulation of these receptors. This presents exciting opportunities for rational rather than serendipitous discovery of therapeutics for schizophrenia.

Background

The introduction of several new antipsychotic drugs in the last decade promised to treat schizophrenia more efficaciously than conventional antipsychotics, and without the unwanted side effects. These drugs, which were modeled after clozapine, reduce dopamine receptor function. However, a discouraging outcome of treatment with these drugs is emerging: they do not substantially improve clinical outcome for schizophrenia and, worse, some produce dangerous side effects, such as weight gain, diabetes, and elevations in blood lipids. There is now an increasing awareness that to move the status of schizophrenia treatment forward, truly novel therapeutic options must be considered (Hyman and Fenton, 2003).

Schizophrenia is characterized by failures in nearly all aspects of higher-order behavior (Hirsch and Weinberger, 2003), including (1) disruption of information processing and sensory perception, leading to thought disorder, hallucinations, and paranoia; (2) abnormal mood affect, influencing a host of behaviors ranging from social interaction to personal hygiene; (3) profound cognitive impairments that encompass most aspects of cognition, including attention, short-term memory, and behavioral flexibility; and (4) movement abnormalities, including stereotypy, catatonia, echopraxia, abnormal posture and limb movements, which are generally ignored because they are not included in current diagnosis criteria. Although different schools of thought have emphasized varying sets of symptoms as the “core” of the disease and have implicated different brain regions as the primary site of pathology, our current understanding of behavioral and systems neuroscience dictates that such a multifaceted failure of normal behavior must involve most, if not all, frontal cortical systems, the limbic system, the basal ganglia, and the thalamus. Reciprocal connections between corticocortical, corticolimbic, and corticothalamic projections are exclusively glutamatergic. In addition, efferents from all cortical areas, as well as key corticolimbic regions such as the hippocampus and amygdala, to motor effector sites are glutamatergic. Glutamatergic neurons are, therefore, the exclusive means by which aberrant information is transferred within and between these regions. In fact, recent postmortem and genetic linkage studies have strongly implicated excitatory neurotransmission in schizophrenia. The glutamatergic system is, therefore, emerging as a promising and mechanistically relevant novel therapeutic target.

Evidence for Excitatory Neurotransmission Involvement in Schizophrenia

Abnormal CSF levels of glutamate and postmortem glutamate receptor binding in schizophrenic individuals have been reported since the 1970s. However, the limitations of these crude measures prevented them from being taken seriously. The glutamate theory of schizophrenia was brought into the mainstream as a result of more sophisticated analysis of postmortem brains of schizophrenics (e.g., Deakin et al., 1989; Clinton et al., 2002; for a recent review, see Konradi and Heckers, 2003) and the discovery that the potent psychotomimetic drug phencyclidine (PCP) is an antagonist of the NMDA subtype of glutamate receptor (Javitt and Zukin, 1991). Phencyclidine, introduced in the 1950s as a dissociative anesthetic, caused postoperative hallucinations and psychosis. In patients with schizophrenia, PCP led to profound exacerbation of pre-existing symptoms. Recent clinical trials in healthy volunteers using the PCP analog ketamine have further established that NMDA antagonist treatment produces transient psychosis, disrupted affect, and cognitive deficits that are similar to those observed in schizophrenia (Krystal et al., 1994; Newcomer et al., 1999; Lahti et al., 2001). Animal studies using selective pharmacological ligands or transgenic manipulation of NMDA receptor subunits also indicate a role for NMDA receptors in a wide spectrum of behaviors that are relevant to schizophrenia (Moghaddam and Adams, 1998; Mohn et al., 1999). The impressive aspect of both basic and clinical findings with NMDA antagonists is that administration of a single dose of the antagonist is sufficient to produce these behavioral effects. Other treatments that produce schizophrenia-like symptoms in humans and animals generally involve chronic treatments, lesions, or mutations. This suggests that transient changes in the functional state of the NMDA receptor may be sufficient for expression of schizophrenia-like symptoms.

A transient disruption in NMDA receptor function is, in fact, an ideal mechanism to underlie the profound behavioral abnormalities observed in schizophrenia. NMDA receptors are ion channels that are coincidence detectors because they are gated simultaneously by voltage and two ligands, glutamate and glycine. Relatively subtle disruptions in mechanisms that influence either membrane potential or ligand binding to various regulatory sites on the receptor may have a profound effect on the probability and duration of NMDA channel opening and, therefore, on behaviors that are modulated by NMDA receptors. Examples of factors that directly influence the function of the NMDA receptor are depicted in Figure 1. These include several regulatory sites on the NMDA receptor itself; presynaptic mechanisms...
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Figure 1. Schematic Illustration of Some of the Components of the Excitatory Synapse and Potential Sites for Pharmacological Intervention in Schizophrenia

Recently described schizophrenia susceptibility genes that can influence the activity of this synapse are depicted in dotted gray circles (see text for details). Some of the targets for pharmacological intervention include the glycine and D-serine binding site on the NR1 subunits of the NMDA receptor, the Glycine transporter (Gly T), and potentiators of metabotropic glutamate (mGlu) receptors, in particular mGlus, which positively modulates NMDA receptors through activation of the G protein Gq, and mGlu2/3, which regulate the release of glutamate.

that regulate the release of glutamate, glycine, and D-serine (an endogenous ligand for the glycine binding site); transporter systems on neurons and glia that regulate synaptic levels of these ligands; and the level of activity of excitatory and inhibitory ion channel receptors such as AMPA and GABAA, that directly influence the membrane potential. In addition, other receptors, such as ErbB4 and mGlus, influence the kinetics of NMDA receptors through interactions with intracellular signal transduction mechanisms and the postsynaptic density (PSD). Thus, even in the absence of any abnormalities in the number or structure of NMDA receptors, dysregulation of any of these regulatory sites may have a profound influence on behavior by disrupting NMDA receptor function in an activity-dependent manner.

Assuming that aberrant NMDA receptor signaling is involved in the pathophysiology of schizophrenia, genes that encode or regulate any of the large number of proteins that influence the function of NMDA receptors would be plausible susceptibility genes for this disease. Recent genetic linkage studies identifying candidate susceptibility genes for schizophrenia support this notion (Harrison and Owen, 2003). For example, neuregulin 1 (NRG1), which has recently been associated with schizophrenia (Stefansson et al., 2002), regulates expression of glutamate receptor subunits and directly activates ErbB4 receptors. This member of the ErbB family of tyrosine kinases is colocalized with the NMDA receptor and is thought to regulate the kinetic properties of the NMDA receptor by phosphorylating the NR2 subunit of the NMDA receptor. Accordingly, mutant mice heterozygous for NRG1 (or ErbB4) display a behavioral profile similar to animals treated with NMDA antagonists and have fewer functional NMDA receptors. Another recently described susceptibility gene is G72, a newly discovered human gene on chromosome 13q34 (Chumakov et al., 2002). G72 interacts with the gene for the enzyme D-amino acid oxidase (DAO), which oxidizes D-serine and thereby reduces its synaptic availability. A third gene that has recently been implicated in schizophrenia is RGS4 (Chowdari et al., 2002). RGS proteins negatively regulate G protein signaling. In particular, RGS4 inhibits signaling by the mGlu5 receptor (Saugstad et al., 1998). This subtype of metabotropic glutamate receptor is localized near the NMDA receptors, and its stimulation potentiates NMDA-mediated currents. The mGlu5-NMDA interaction requires activation of Gq, a G protein that is regulated by RGS4. A fourth example of a recently identified candidate gene is dysbindin (Straub et al., 2002). Dysbindin, through the dystrogin protein complex, recruits molecules such as nitric oxide synthase (NOS) that influence NMDA receptor activity by interacting with PSD. Finally, the PPP3CC gene, which encodes the calcineurin γ subunit, has recently been associated with schizophrenia (Gerber et al., 2003). Calcineurin is critical for certain types of NMDA-mediated plasticity. There are also a number of other related linkage findings, including the GRIN1 gene (Martucci et al., 2003), which encodes the NR1 subunit of the NMDA receptor, and GRM3 (Fuji et al., 2003), the mGlu3 receptor gene, that await replication in larger and more diverse sample sizes.

Clearly, the genes outlined above serve functions that may be unrelated to NMDA receptors. More importantly, these linkage studies are at different stages of replication and have differing degrees of statistical validation. However, it is significant that influencing excitatory neurotransmission appears to be the common link among most recently described susceptibility genes for schizophrenia. This suggests that a complex set of genetic factors produce a similar behavioral syndrome across diverse patient populations through a common functional pathway: the modulation of NMDA receptor function.

Implications for Etiology and Pathophysiology of Schizophrenia

The recent genetic findings begin to rebut the longstanding skepticism that has surrounded the idea of NMDA receptor dysfunction in schizophrenia. This legitimate skepticism arises from the fact that NMDA receptors are ubiquitous and are implicated in a wide range of physiological processes critical to brain function, such as development, plasticity, and excitotoxicity.
normalities in NMDA-mediated neurotransmission might, therefore, be expected to profoundly affect most aspects of brain function beginning at the earliest stages of development rather than causing selective behavioral abnormalities manifested primarily after adolescence, as in schizophrenia. However, the genetic and postmortem findings do not support gross abnormalities at the level of NMDA receptor subunit structure, receptor number, or cellular localization. Rather, the vulnerability to develop schizophrenia now appears to arise from changes in the function of genes that encode proteins which modulate some of the downstream effects of NMDA receptor activation. This suggests that selective and activity-dependent changes in the efficiency of NMDA receptor-mediated signaling, as opposed to colossals disruptions in NMDA receptor function, may be a culprit in schizophrenia.

Considering the well-established involvement of NMDA receptors in neuronal development, the recent findings are also consistent with notions that schizophrenia is a developmental disorder and that epigenetic factors play a major role in the disease process. A disruption in epigenetic regulation of development at critical periods may alter the expression of the vulnerable genes and affect the development of cortical and limbic neurons by modifying NMDA-mediated signal transduction. A large epidemiological literature, in fact, associates environmental factors such as maternal health and birth complications to an increased propensity to develop schizophrenia (Hirsch and Weinberger, 2003). Environmental factors, including stress, which is a profound activator of cortical glutamate pathways (Moghaddam, 2002), are also involved in the onset or exacerbation of symptoms of schizophrenia, suggesting that epigenetic factors may continue to influence the expression of the affected genes in adulthood. Questions, however, remain as to why a disruption in the function of NMDA receptors throughout the brain, albeit subtle, would lead to very selective behavioral abnormalities that are associated with schizophrenia. Despite the ubiquitous nature of NMDA receptors, it is important to keep in mind that administration of low doses of NMDA antagonists produces a behavioral profile in healthy volunteers that is similar to schizophrenia (Krystal et al., 1994). Thus, as our knowledge of the role of NMDA receptors in regulating complex behavior evolves, it may become apparent that reductions in NMDA-mediated signal transduction have a selective influence on cognitive and affective functions that are related to symptoms of schizophrenia. Implication for Treatment

The recent genetic findings are also enticing the field to put more emphasis on developing ligands for modulatory sites that influence the glutamate synapse. The schizophrenia-like effects of NMDA antagonists in healthy volunteers suggest that the primary glutamatergic abnormality in schizophrenia is reduced NMDA function. Therapeutic strategies, therefore, have focused mostly on enhancing NMDA receptor function through mechanisms that positively modulate this receptor (Javitt, 2002). Results of recent clinical trials testing this hypothesis have been promising. At least seven placebo-controlled studies have focused on the strategy of enhancing NMDA receptor function by targeting the glycine modulatory site (Coyle et al., 2002; Tsai et al., 2003). These trials have consistently shown improvement in cognitive functioning and the so-called negative symptoms of schizophrenia when agonists of the glycine site, such as D-serine, D-cycloserine, or n-methyl-glycine, were administered to patients with chronic schizophrenia stabilized on neuroleptics.

The positive results of these clinical trials are facilitating the development of more specific ligands that have shown promise in preclinical models. Among these are the following. (1) Specific blockers of the glycine transporter (Javitt, 2002), which would be expected to increase the synaptic levels of glycine and enhance NMDA-mediated functions. (2) Positive modulators of mGlu5 receptors, a group of metabotropic glutamate receptors that synergistically enhance NMDA receptor-mediated currents. Recent behavioral data with systemically active ligands of mGlu5 receptors suggest that the molecular and cellular interaction between NMDA and mGlu5 receptors extends to regulation of complex behavior (Kinney et al., 2003). Because of the rapid rate of mGlu5 receptor desensitization, mGlu5 receptor agonists are not considered to be effective therapeutic targets; however, allosteric sites on the receptor that positively modulate its function have recently been discovered (Knoflach et al., 2001). Potentiators of these sites are now considered to be important candidates for positive modulation of NMDA receptor function and treatment of schizophrenia. (3) Agonists of mGlu2/3 receptors, another group of metabotropic glutamate receptors that autoregulate the release of glutamate and were found to normalize the behavioral effects of NMDA antagonists (Moghaddam and Adams, 1998). Recent clinical trials in healthy volunteers show that treatment with an mGluR2/3 agonist reduces schizophrenia-like cognitive deficits induced by ketamine (Krystal et al., 2003), suggesting that potentiation of mGlu2/3 receptor function may be an effective treatment strategy for the cognitive symptoms of schizophrenia. Clinical trials in schizophrenia, at least as an adjunct therapy, may not be far in the future.

Conclusions

Given the accumulating literature implicating glutamatergic dysfunction in schizophrenia, there is great optimism that basic and clinical researchers will take advantage of the available animal models and the large number of modulatory targets on NMDA and related receptors to design and test treatment strategies that could fine tune abnormal glutamate neurotransmission in schizophrenia. This approach represents a conceptual shift in a field that remains firm in the belief that a hyperdopaminergic state is the primary culprit in schizophrenia. Dopamine D2 receptor antagonists are, in fact, the only known effective treatment for psychosis. However, postmortem and genetic studies have generally failed to show abnormalities with the D2 receptor. In addition, the simple idea that an overactive dopamine system elicits psychosis is not supported by the fact that dopamine D1 antagonists, which are far more effective than D2 antagonists in blocking hyperdopaminergic behavioral states in laboratory animals, do not alleviate but may even exacerbate psychosis. This worsening of symptoms, on the other hand, is consistent with an NMDA-deficient state in schizophrenia, because a consequence of reduced NMDA receptor activity may be
downregulation of D1 receptors (Scott et al., 2002). A characteristic that distinguishes the D2 receptors from D1 receptors is that D2 receptors can regulate glutamate release from corticolimbic and corticostriatal terminals by virtue of their presynaptic localization on these terminals (Wang and Pickel, 2002). After decades of unsuccessful attempts to connect the dots from the clinical efficacy of D2 receptor antagonists to the pathophysiology of schizophrenia, it may be that D2 antagonists have been simply fine tuning the output of glutamate neurons in key cortical and limbic regions. Only future clinical trials using direct manipulation of the glutamate system will tell.

Selected Reading


