Cognitive Dysfunction in Schizophrenia

Convergence of γ-Aminobutyric Acid and Glutamate Alterations

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Impairments in certain cognitive functions mediated by the dorsolateral prefrontal cortex, such as working memory, are core features of schizophrenia. Convergent findings suggest that these disturbances are associated with alterations in markers of inhibitory γ-aminobutyric acid and excitatory glutamate neurotransmission in the dorsolateral prefrontal cortex. Specifically, reduced γ-aminobutyric acid synthesis is present in the subpopulation of γ-aminobutyric acid neurons that express the calcium-binding protein parvalbumin. Despite presynaptic and postsynaptic compensatory responses, the resulting impaired inhibitory regulation of pyramidal neurons contributes to a reduction in the synchronized neuronal activity that is required for working memory function. Several lines of evidence suggest that these changes may be either secondary to or exacerbated by impaired signaling via the N-methyl-D-aspartate class of glutamate receptors. These findings suggest specific targets for therapeutic interventions to improve cognitive function in individuals with schizophrenia.

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nia, determining the nature of the underlying disturbances in DLPFC circuitry is essential for the identification of new drug targets.

Although other neurotransmitter systems are certainly involved, findings from a number of investigations suggest that disturbances in inhibitory γ-aminobutyric acid (GABA)–mediated or excitatory glutamate-mediated neurotransmission may contribute to the cognitive impairments of schizophrenia. In this article, we briefly review this evidence, consider the potential relationships that may exist between the GABA and glutamate abnormalities, and discuss the implications of these findings for pharmacological interventions to improve cognitive performance in individuals with schizophrenia.

ALtered GABA NeUrotransmission and COgnitive disturbanCes in Schizophrenia

Working memory depends on the coordinated and sustained firing of subsets of DLPFC pyramidal neurons between the temporary presentation of the stimulus cue and the later initiation of the behavioral response, and fast-spiking GABA neurons in the DLPFC seem essential for such synchronization of pyramidal neuron activity. These findings suggest that impairments in GABA-mediated inhibition in the DLPFC could contribute to the impairments in working memory present in schizophrenia. Consistent with this interpretation, reduced expression of GAD67 mRNA for the 67-kDa isoform of glutamic acid decarboxylase (GAD67), an enzyme that synthesizes GABA, is one of the most consistent findings in postmortem studies of individuals with schizophrenia. The mRNA expression of GAD67 is undetectable in a subset of DLPFC GABA neurons, whereas most GABA neurons have normal levels of GAD67 mRNA. Furthermore, in the same individuals, the mRNA expression for the GABA membrane transporter (GAT1), a protein responsible for the reuptake of released GABA into nerve terminals, is similarly decreased in a subpopulation of DLPFC GABA neurons. Thus, the synthesis and reuptake of GABA are reduced in a subset of DLPFC inhibitory neurons in schizophrenia.

The affected GABA neurons include those that contain the calcium-binding protein parvalbumin (PV), which is present in approximately 25% of GABA neurons in the primate DLPFC, whereas the approximately 50% of GABA neurons that express the calcium-binding protein calretinin (CR) are unaffected. The PV-positive (PV+) neurons are also distinguishable from other cortical GABA neurons by their fast-spiking, nonadapting, firing pattern, and subsets of these neurons can be identified by their morphological features. For example, the axons of the chandelier subclass of PV+ GABA neurons give rise to linear arrays of terminals (termed cartridges) that synapse exclusively on the axon initial segments of pyramidal neurons. In the DLPFC of subjects with schizophrenia, the density of chandelier neuron axon cartridges immunoreactive for GAT1 is significantly reduced, whereas immunoreactivity for GAT1 in other populations of axon terminals is unchanged. In concert, these findings suggest that chandelier neurons in the DLPFC of subjects with schizophrenia express decreased levels of PV mRNA and undetectable levels of GAD67 and GAT1 mRNAs, with the latter resulting in reduced GAT1 protein in the axon cartridges of these neurons. In addition, the density of pyramidal neuron axon initial segments immunoreactive for the GABA type A (GABA_A) α2 subunit is markedly increased in schizophrenia, apparently reflecting higher levels of α2 subunits in the axon initial segment. These changes are not found in subjects with other psychiatric disorders or in monkeys exposed long term to antipsychotic medications, suggesting that they are specific to the disease process of schizophrenia. Thus, in the DLPFC of subjects with schizophrenia, GABA_A receptors are up-regulated at pyramidal neuron axon initial segments in response to deficient GABA release from chandelier neuron axon terminals.

Understanding the contribution of these abnormalities to the cognitive deficits in schizophrenia depends on the demonstration of a pathophysiological process by which reduced chandelier cell inputs to pyramidal neurons could give rise to working memory impairments. Networks of PV+ fast-spiking GABA neurons, formed by chemical and electrical synapses, give rise to oscillatory activity in the β-band range, the synchronized firing of a population of neurons at 30 to 80 Hz. Interestingly, β-band oscillations in the DLPFC increase in proportion to working memory load, and in subjects with schizophrenia, DLPFC β-band oscillations are reduced during the delay period of a working memory task. Thus, a deficit in the synchronization of pyramidal cells, resulting from impaired inhibition by PV+ GABA neurons, might contribute to reduced β-band oscillations and, consequently, to working memory dysfunction in subjects with schizophrenia.

Glutamate neurotransmission and cognitive disturbances in schizophrenia

Glutamate mediates fast excitatory postsynaptic potentials by acting on the ionotropic receptors: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate. Glutamate also exerts modulatory effects by acting on different subtypes of G protein–coupled metabotropic glutamate (mGlu) receptors. For example, the group 5 mGlu receptors (mGlu5) potentiate the duration of NMDA receptor–dependent excitatory postsynaptic potentials, whereas mGlu2 and mGlu3 receptors modulate the release of glutamate. The glutamate synapse is also influenced by efficient excitatory amino acid transport proteins on glial cells and by a host of molecules that influence glutamate receptor trafficking and the intracellular signaling machinery associated with postsynaptic density.

The following lines of evidence implicate these glutamate receptors and glutamate receptor–associated molecules in the pathophysiological features of schizophrenia (reviews have been performed by several researchers). First, postmortem studies show significant, albeit modest, changes in glutamate receptor binding, transcription, and subunit protein expression in the PFC, thalamus, and hippocampus of subjects with schizophrenia.

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schizophrenia. These include decreases in the NR1 subunits of the NMDA receptor in the hippocampus and DLPFC, decreased AMPA receptor expression in the hippocampus, high expression of excitatory amino acid transport in the thalamus, decreased kainate receptor binding in the DLPFC, and robust changes in the NMDA and AMPA receptor–affiliated intracellular proteins, such as postsynaptic density protein 95 and synapse-associated protein 102, in the DLPFC and thalamus.

Second, levels of the amino acids N-acetylaspartate and N-acetylaspartylglutamate, and the activity of the enzyme N-acetyl-L-linked acidic peptidase, which cleaves N-acetylaspartate to N-acetylaspartylglutamate and glutamate, are altered in the cerebrospinal fluid and brain specimens of subjects with schizophrenia. N-acetylaspartylglutamate is an endogenous ligand for the mGlu3 subtype of mGlu receptors. Furthermore, reduced N-acetylaspartate levels are thought to reflect decreased glutamate availability.11

Third, many of the genes recently associated with an increased risk for schizophrenia can influence the function of modulatory sites on the NMDA receptor or intracellular-receptor interacting proteins that link glutamate receptors to signal transduction pathways.23,24 These genes include neuregulin 1, which can influence the expression of NMDA receptors through activation of ErbB4 receptors; and the type 3 metabotropic glutamate receptor gene, which encodes the mGlu3 subtype of mGlu receptors.

Fourth, exposure to NMDA receptor antagonists, such as phencyclidine or ketamine, produces “schizophrenia-like” symptoms in healthy individuals and profoundly exacerbates preexisting symptoms in patients with schizophrenia.28 In particular, direct comparison of healthy volunteers receiving subanesthetic doses of ketamine and of individuals with schizophrenia reveals similar disruptions in working memory and thought disorder.27

Together, these findings strongly suggest that deficient activation of NMDA receptors may be a critical component of the cognitive deficits of schizophrenia. This conclusion is consistent with a large body of animal studies suggesting that NMDA receptors within the PFC are critical for sustaining working memory and other cognitive functions that are impaired in schizophrenia.28

WHAT IS THE RELATIONSHIP BETWEEN ALTERED GABA AND GLUTAMATE NEUROTRANSMISSION IN SCHIZOPHRENIA?

Because the activity of cortical GABA neurons is, in part, regulated by glutamate inputs, the alterations in GABA neurotransmission might reflect an abnormal glutamatergic drive onto these neurons. For example, the deficit in GAD67 mRNA expression could represent an activity-dependent change in response to reduced glutamatergic activity in projections to the DLPC from the thalamus19 or hippocampus.29 However, given the ubiquitous nature of glutamate neurotransmission, a critical question is why changes in glutamate function might differentially affect the PV+ and, not the CR+ (PV+), subclass of GABA neurons. Interestingly, the glutamatergic drive seems notably stronger to PV+ than CR+ neurons (Figure). First, PV+ cells receive a larger complement of excitatory inputs. In the rodent hippocampus, the total number of excitatory synapses onto PV+ neurons is nearly an order of magnitude greater than the number onto CR+ neurons.30 Consistent with these observations, the density of excitatory synapses on PV+ dendrites in monkey DLPFC is significantly greater than on CR+ dendrites, although the magnitude of the difference is less striking than in rodent hippocampus.31

Second, subpopulations of GABA neurons differ in the complement of glutamate receptor subunits that they express. In the human temporal cortex, approximately 90% of PV+ cells, but only 20% of CR+ cells, are immunoreactive for the glutamate receptor 1 subunit, and this ratio is nearly completely reversed for the glutamate receptor 2 or 4 subunit.32 Across regions of monkey neocortex, immunoreactivity for the NR1 subunit was detected in most (50%-90%) PV+ neurons, but in less than 10% of CR+ neurons,33 although the difference between these cell types was less marked in the human temporal cortex.34

Third, PV+ GABA neurons are particularly sensitive to the effects of NMDA receptor antagonists, suggesting a high level of NMDA receptor tonic activation in these neurons. For example, following long-term phencyclidine exposure, the expression level of PV mRNA per neuron was decreased by 25% in rat PFC, but the density of PV mRNA–positive neurons was unchanged.35 These findings are strikingly similar to the pattern of PV mRNA expression changes observed in the DLPFC of subjects with schizophrenia.31 Taken together, these findings suggest that the alterations in GABA neurotransmission selective for PV+ neurons might be a downstream consequence of impaired NMDA receptor–mediated glutamatergic inputs to these neurons.

TREATMENT IMPLICATIONS

The value of understanding these alterations in GABA and glutamate neurotransmission in schizophrenia rests in the extent to which they inform the identification of novel targets for pharmacological intervention. Although dopamine D2 receptor antagonists effectively suppress the psychotic features of schizophrenia, typical antipsychotic drugs might, in fact, impair cognitive functions.35 Furthermore, while atypical antipsychotic drugs, which target several subtypes of dopamine and serotonergic receptors, may improve cognitive function, this effect is relatively small and has not been reproducible across laboratories.36 Thus, research aimed at the improvement of cognitive symptoms must move beyond monoamine-based treatment strategies.

The following glutamate receptor–related strategies have been proposed to mitigate deficient glutamate neurotransmission in schizophrenia.12,37 First, a class of drugs called ampakines reduces the rapid rate of desensitization of AMPA receptors and, hence, prolongs AMPA- and NMDA-mediated excitatory postsynaptic potentials. Preliminary trials8,30 of ampakines in patients with schizophrenia have produced mixed results, but larger clinical trials are under way. Second, positive modulation of the NMDA receptor by stimulating the glycine site on the NMDA channel has been tried,31 including direct activation of this site
by endogenous or exogenous agonists. These clinical trials have also produced mixed results, but the relative lack of specificity and solubility of the drugs used limits the interpretation of these studies. Animal work with more specific glycine site agonists or glycine transporter blockers suggests that these drugs may be effective in ameliorating the adverse effects of NMDA deficiency. Third, mGlu2 or mGlu3 agonists reduce the working memory deficits elicited by NMDA antagonists, but the effects of these drugs on cognitive functions in schizophrenia have not yet been evaluated. Fourth, animal studies suggest that tonic stimulation of mGlu5 receptors is critical for working memory functioning. This class of receptors also plays a critical role in burst activity of PFC neurons and enhances the function of NMDA receptors. Although ligands that allosterically enhance the function of mGlu5 receptors are only in the preclinical developmental stages, this class of modulators holds promise for improving working memory dysfunction associated with NMDA receptor deficiency.

If, as previously suggested, reduced GABA neurotransmission in PV+ neurons is secondary to altered NMDA receptor function, then abnormal GABA neurotransmission could represent a “final common pathway” to prefrontal dysfunction in schizophrenia. Thus, drugs targeted to mitigate the disturbances in inhibition might be particularly effective in improving cognitive performance in schizophrenia. For example, positive allosteric modulators selective for GABAα1 receptors containing α2 subunits (eg, a GABAα1α2-selective benzodiazepine), by enhancing the response of pyramidal neurons to the release of GABA from PV+ chandelier cell axons, would
be predicted to increase the synchronization of pyramidal cell firing at γ frequencies and, thus, improve working memory function in schizophrenia.10 In contrast, drugs that directly activate α2-containing GABA_A receptors independent of the presence of GABA or those that generally increase the firing rate of chandelier cells might disrupt the critical timing of inhibition necessary to synchronize pyramidal neuron firing. In addition, available benzodiazepines have activity at GABA_A receptors containing other subunits (eg, α1 or α2) whose activation can impair cognitive function.

In conclusion, advances in understanding the pathophysiology of cognitive dysfunction in schizophrenia are providing a rational basis for the development of novel pharmacological interventions that may improve the long-term functional outcome of individuals with schizophrenia.

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