The Neurobiology of Cognition in Schizophrenia

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Currently, no drugs exist that effectively treat cognition in people with schizophrenia. What is known about the neurobiology of cognition in schizophrenia is derived from the animal literature; it is inadequate and superficial. Despite this lack, pharmacologic research into potential molecular targets has uncovered several viable possibilities from animal studies. A subcommittee of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program investigated the range of putative molecular targets for treating cognition. Those targets that show promise for pharmacologic focus include the dopamine receptors (especially D_1) in the prefrontal cortex (PFC), the serotonin receptors in the PFC and anterior cingulate cortex, the glutamatergic excitatory synapse, the acetylcholine nicotinic receptors in the hippocampus, the acetylcholine muscarinic receptors, and the brain γ-aminobutyric acid (GABA) system. Once developed and tested, the effective compounds will be valuable for the treatment of the symptom domains of cognitive dysfunction and negative symptoms.
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Currently, no drugs exist that effectively treat cognition deficiencies in people with schizophrenia. What is known about the neurobiology of cognition in schizophrenia is predominantly derived from animal studies, which are inadequate and imprecise. However, several possibilities exist for new pharmacologic and psychological treatments that have been developed from animal studies. The molecular targets of these new treatments include the dopamine-1(D_1) receptors, the serotonin system, the glutamatergic system, the nicotinic receptors, the cholinergic system, and the brain γ-aminobutyric acid (GABA) system. Because of the lack of progress over the last half century in developing new treatments for schizophrenia, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program was organized to help researchers discover, target, and develop compounds that act on cognition and may become potential treatments for schizophrenia.

THE NEUROBIOLOGY OF COGNITION

The first MATRICS committee was charged with identifying cognitive targets and establishing criteria for test selection.[1] They identified 7 different domains of dysfunction in patients with schizophrenia: verbal learning and memory, speed of processing, working memory, reasoning and problem solving, attention and vigilance, visual learning and memory, and social learning.[2] By defining separate cognitive deficits, researchers may be better able to target a treatment for each one and/or to develop general cognitive-enhancing compounds.

A second MATRICS committee focused on neuropsychopharmacologic approaches to modulating cognition in schizophrenia and identified pharmacologic strategies and promising compounds for treating cognition.[1] These targets include the dopamine receptors in the prefrontal cortex (PFC), the serotonin receptors in the PFC and anterior cingulate cortex, the glutamatergic excitatory synapse, the acetylcholine nicotinic receptors in the hippocampus, the acetylcholine muscarinic receptors, and the brain GABA system.

Cognitive dysfunction in schizophrenia appears to be different compared with cognitive dysfunctions in other diseases of cognition, such as bipolar disorder or Alzheimer's dementia. Cognitive dysfunction in dementia derives from dying neurons and from a consequent reduction in neuronal activity, but research[3] in schizophrenia has shown that cognitive dysfunction derives from neuronal dysfunction, not from neurodegeneration. In postmortem tissue studies in schizophrenia, there is no neuronal loss even if volume is altered.[4] The limbic circuit may be important in mediating cognitive symptoms in schizophrenia and may harbor disease pathophysiology. The PFC, the parietal cortex, the anterior cingulate cortex, the hippocampus, and the basal ganglia have a substantial role in declarative memory. Learning and memory systems, regions mediating executive function, and attention systems in the brain are located mainly in the PFC, anterior cingulate cortex, and medial temporal lobe.

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PHARMACOLOGIC SYSTEMS

An understanding of brain regions and their neuropharmacologic systems may help researchers establish hypotheses about the mechanisms of abnormalities that may underlie cognitive dysfunction and identify drug candidates for testing. While a number of already well-developed techniques for assessing the actions of drugs and cognition in animals have been established, methods for testing these in humans are wanting. And while assessments for establishing neuropsychological performance are routine, the ability to evaluate functioning in daily life is also wanting.

Dopamine System

The D_1 family of dopamine receptors is likely to be more directly involved in cognition than the D_2 family of dopamine receptors, which are studied for their role in psychosis. The D_1 family of dopamine receptors is located in relatively high density on the distal dendrites of the PFC pyramidal neurons. These receptors are also located on the terminals of the intracortical pyramidal projections, which have afferent and efferent distal projections, and on GABA-containing interneurons in the PFC, which facilitate feed-forward inhibition. D_1 receptors have many recurrent collateral and intracortical connections so that the pyramidal neurons remain connected with themselves and with other regions of the brain.

Pharmacology. Information drawn from animal tests suggests that D_1 receptors are important for modulating working memory and that D_1 agonists improve and antagonists degrade working memory performance. Research by Goldman-Rakic et al.[5] suggests that D_1 receptors are associated with the regulation of the PFC microcircuitry to modulate working memory and that D_1 but not D_2 antagonists disrupt memory when directly applied to the PFC. Compared with D_1 receptors, concentrated densely in the PFC, the density of D_2 receptors is so low that they can only be measured with great difficulty. Animal tests[5] have confirmed the positive effect of D_1 agonists on the PFC, showing that D_1 agonists correct age-associated memory deficits in animals. D_1 agonists have been found to increase the strength of the PFC memory field in primates, while age-related deficits in cognition in rats correlate with age-associated markers of dopamine reduction in the PFC but not in the striatum.

Promising compounds for potential treatments. Although several molecular targets have been identified, few compounds are yet available to be tested in humans. The use of direct-acting D_1 agonists in humans is difficult because D_1 receptors are located on the peripheral vasculature system. Because D_1 agonists have the potential to be powerful hypotensive agents in human tests, identifying a viable candidate has been difficult. Three dopamine activating compounds of research interest are DAR 100, tolcapone, and atomoxetine.

DAR 100. DAR 100 is a direct-acting D_1 agonist that, if given intravenously, causes profound hypotension, but can be used as a probe for D_1 receptors if given subcutaneously. It is being evaluated as a probe to establish the viability of this molecular target for improving cognition. DAR 100 may serve as a valuable research tool, but only possibly as a therapeutic compound.

Tolcapone. Tolcapone is a selective catechol-*O*-methyltransferase inhibitor and indirect dopamine agonist in the PFC. This agent is used in the treatment of patients with Parkinson's disease. Research by Weinberger et al.[6] showed that tolcapone influences neuronal activation, as measured by in vivo imaging in the PFC. Treatment with tolcapone for patients with schizophrenia could be beneficial, and further study is ongoing.

Atomoxetine. Atomoxetine is a norepinephrine reuptake blocker and an indirectly acting dopamine agonist in the prefrontal cortex that increases tissue levels of norepinephrine and dopamine. Currently, the drug is approved for attention-deficit/hyperactivity disorder and is being evaluated in schizophrenia.

Serotonin System

Of the approximately 15 serotonin receptors for the serotonin system, the 5-HT_{1A}, the 5-HT_{2A}, and the 5-HT_6 have been identified as potentially important in cognition. Other serotonin receptors may be important as well, but current research is focusing on these three. The cell bodies of the serotonin system are located in the dorsal raphae. From the dorsal raphae, the serotonin system fans out to innervate the limbic cortex, the neocortex, and many parts of the basal ganglia.

5-HT_{1A} receptor. The 5-HT_{1A} receptor is densely concentrated in the hippocampus, the cingulate, and the raphae (in the latter as an autoreceptor). But, its concentration in the hippocampus has raised the possibility that it might be associated with declarative memory. The stimulation of the 5-HT_{1A} receptor inhibits pyramidal neurons in the hippocampus. Since the function of the autoreceptor in the raphae is to regulate the release of serotonin in the distal projection fields, a drug that acts in the raphae can affect the levels of serotonin that are released in the whole neocortex.

Both 5-HT_{1A} partial agonists and full antagonists have shown a positive effect on cognitive activity in animals, but because they act on different locations of the receptors, they could be working in different ways. Partial 5-HT_{1A} agonists act on the pyramidal neurons, and they improve cognition in animals. In addition, 5-HT_{1A} full antagonists can also improve cognition, probably by acting at the raphae autoreceptors. Two 5-HT_{1A} compounds under investigation as serotonin-based treatments for cognition include tandospirone, a partial agonist, and an Avera compound 645, a full antagonist.

5-HT$_{2A}$ receptor. The 5-HT$_{2A}$ receptor is concentrated in layer 5 of the cortical pyramidal neurons, usually located with *N*-methyl-D-aspartate (NMDA) glutamate receptors, and it is also located on dopamine neurons in the ventral tegmental area. This receptor modulates both glutamate and dopamine neuronal activity and glutamate and dopamine release. The role that 5-HT$_{2A}$ antagonism plays in the modulation of dopamine neuronal activity has been highly investigated and is still contested. Pharmacology studies in animals suggest that 5-HT$_{2A}$ antagonism decreases the release of dopamine in the basal ganglia.[7] However, results have been mixed. Nonetheless, 5-HT$_{2A}$ antagonists have been shown to improve cognition in animals, and 5-HT$_{2A}$ agonists impair cognition in animals. Two 5-HT$_{2A}$ compounds available for testing cognition enhancement are MDL 100907, which is the first pure serotonin 5-HT$_2$ antagonist and shows mild antipsychotic activity, and ACP-103, a drug whose action is similar to MDL 100907.

5-HT$_6$ receptor. The 5-HT$_6$ serotonin receptor is an attractive receptor to investigate in cognition because there is not much known about its function. The 5-HT$_6$ receptor is located in high concentration in the olfactory cortex, neocortex, limbic striatum, and hippocampus. Both clozapine and olanzapine show high affinity for the 5-HT$_6$ receptor. These drugs are 5-HT$_6$ inverse agonists that function to increase acetylcholine release. Researchers hypothesize that, through the increased cholinergic activation, 5-HT$_6$ antagonists may improve cognition in schizophrenia.[7]

The Glutamatergic Excitatory Synapse

Because glutamate is powerfully involved in modulating long-term potentiation, a model for learning and memory, it is most likely involved with human neuroplasticity and cognition. Modulating glutamate pharmacologically has long been advocated for improving cognition. The glutamate system, especially its NMDA-dependent components, is complex and offers multiple targets for possible cognitive enhancement in schizophrenia. Small increases in NMDA-dependent glutamate transmission might be cognitively enhancing, whereas if synaptic activity is increased too much, neurodegeneration could result. At the glutamatergic excitatory synapse, presynaptic release or postsynaptic agonism could act correctly. Many signaling proteins in the postsynaptic region could be targeted to enhance glutamatergic signals, as well.

Enhancing the glutamate-glutamine cycle in astrocytes could also modulate the glutamatergic synapse. Glutamate released from the presynaptic neuron, after it stimulates the postsynaptic receptor, is taken up by the astrocytes. From the astrocytes, the glutamate is converted to glutamine and then cycles back into the presynaptic site.

Pharmacology. Several pharmacologic approaches involving glutamate that have explored cognition in animals include enhancement of function at ionotropic receptors and at α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and NMDA receptors such as the ampakines. Enhancement of activity at ionotropic receptors could improve human cognition, but excitotoxicity would be a potential danger. The AMPA and NMDA receptors work cooperatively. The AMPA receptor is the main excitatory signaling receptor, and the NMDA receptor is voltage-gated and augments the signal from the AMPA receptor. Ionotropic antagonists appear to impair aspects of cognition in animals; similarly, in humans, antagonists such as ketamine, phencyclidine, and MK-801 worsen cognition. Antagonists at glutamate receptors would enhance cognition, if any could be found that could be safely used.

The metabotropic receptors mGluR5 and mGluR 2/3 modulate the information carried in the ionotropic signal and may hold promise as treatment targets for cognition, because the agonists at both of these sites seem to improve cognition in animals. Studies of allosteric modulators of the mGluR5 seem promising but are too incomplete to make any final determination; the mGluR 2/3 agonists improve cognition by normalizing glutamate release.[8]

Treatments based on glutamate. Treatments based on glutamate, such as the ampakines, which mildly enhance glutamatergic action in the synapse, are attractive in cognition research because their action on the glutamatergic synapse is often linked to effective treatment. Increasing precursor activity might increase transmission at the glutamate synapse. Research[9] has shown positive activity of glycine and D-cycloserine, especially on negative symptoms of schizophrenia. But, a recent study[10] with glycine and D-cycloserine was negative, which may suggest discouragement to the use of the drugs rather than to the strategy. Despite these results, there are different ampakines, and another glutamate compound might show a positive effect.

Acetylcholine Nicotinic Receptors

Preclinical data[11] suggested that acetylcholine plays a substantial role in cognition. Nicotinic receptors are located in highest density in the human hippocampus and seem to be important in the activity of the hippocampus. These receptors are ionotropic receptors, have a pentameric receptor, and also have α (e.g., α_2 through α_9) and β (e.g., β_2 through β_4) subunits. The two most prevalent nicotinic receptors are the α_4/β_2, which is a high affinity receptor, and the α_7, which is a low affinity nicotinic receptor. Nicotinic receptors appear to modulate neurotransmitter release, thereby improving cognition, which means that the nicotinic receptor is a modulatory receptor with respect to cognition.

The pharmacology of the nicotinic receptor suggests that it might be active in schizophrenia. Patients with

schizophrenia are heavy cigarette smokers[12]; in addition, patients with schizophrenia have a deficit in auditory gating,[13] a function regulated by the nicotinic receptor. Research by Martin et al.[14] has shown that functional polymorphisms exist in the promoter region of the α_7 receptor and that there is decreased α_7 receptor binding in the schizophrenic brain. Alterations in α_4/β_2 receptor binding have been found in the schizophrenic brain, mainly in the hippocampus.

Research[15] on nicotine treatment of individuals with schizophrenia has shown that, in single administrations, nicotine improves some aspects of cognition (e.g., working memory and declarative memory). However, only single administrations of nicotine improve some aspects of cognition—second administrations are not effective, because tachyphylaxis quickly occurs. Therefore, nicotine would never be an effective treatment, but treatment with partial agonists (e.g., the partial nicotinic agonists GTS-21 and TC-1734), which have a decreased intrinsic activity at the receptor but also a lower propensity to produce tachyphylaxis, are being investigated.

Acetylcholine Muscarinic Receptors

Research[11] showed that muscarinic (M_1) receptors, which are located in high concentrations in the basal cholinergic complex and around the nucleus of the Meynert-cortical path, are reduced in the PFC of patients with schizophrenia. The Meynert-cortical pathway is the route by which acetylcholine is delivered to the neocortex to modulate neuronal activity in the neocortex. Receptors are located throughout the limbic cortex, the neocortex, and the subcortical regions. However, lesions of the cholinergic pathway produce cognitive deficiencies, which is involved in the mechanism for dementia in Alzheimer's disease. Animal studies[16–18] in which cognitive deficiencies are produced by lesions have shown that cognitive deficits can be restored by using cholinergic agonists (e.g., physostigmine).

Treatments based on muscarinic receptors are acetylcholinesterase inhibitors, muscarinic agonists, and allosteric modulators. Administration of muscarinic antagonists (e.g., atropine and scopolamine) alone has been found to impair cognition in animals and in humans.[19]

Acetylcholinesterase inhibitors. Acetylcholinesterase inhibitors, indirect-acting cholinergic agonists used in the treatment of Alzheimer's disease, have a minimal effect in patients with schizophrenia.

Muscarinic agonists. Xanomeline, an agonist at all of the muscarinic receptor subtypes M_1 through M_4, has been shown to have some antipsychotic activity and produce improvements in cognitive dysfunction in patients with schizophrenia.[20,21] Because xanomeline affects all 4 subtypes instead of just the M_1 receptor, it has severe and rate-limiting side effects. Other muscarinic agonists are being developed now that would be selective M_1 agonists.

Muscarinic allosteric modulators. Muscarinic allosteric modulators, such as *N*-desmethylclozapine (the major active metabolite of clozapine), are selective to the M_5 receptors and produce $M_{1/5}$ agonist activity without M_2, M_3, or M_4 activity and side effects.[22,23]

The Brain GABA System

The brain GABA system has been previously investigated for the treatment of tardive dyskinesia. At that time, measuring cognition was not considered, which has limited the amount of available data on the effects of GABA agonists on cognition in people with schizophrenia. GABA agonists do not affect psychosis and are beneficial for motor disorders such as tardive dyskinesia. Recent observations[24–26] have noted decreases in glutamic and decarboxylase 67 (GAD67) messenger RNA (mRNA), the synthetic enzyme for GABA, suggesting that GABA itself is reduced in the cortex in schizophrenia. This decrease in GAD67 is not widespread in every GABA-containing interneuron but rather is restricted to the parvalbumin-positive neurons, which suggests that the defect in GABA in the PFC is relatively selective.

Research by Lewis et al.[27] has shown an increase in GABA receptor production, particularly the α_2 subunit, in the PFC in postmortem brain tissue from cases with schizophrenia. Based on these data, one can predict that GABA agonists that show an affinity at the α_2 subunit of the GABA receptor will have cognitive-enhancing activity in schizophrenia. While a number of compounds are currently available that are not direct-acting GABA agonists, inverse agonists are being tested for improving cognition in patients with schizophrenia. These compounds have been tested for the treatment of anxiety, so their pharmacology is understood, but studies on the pharmacology of cognition in patients with schizophrenia are needed.

CONCLUSION

Strategies for treating patients with schizophrenia are changing so that, in the future, medications may be available that target cognitive domains (e.g., psychosis, cognitive dysfunction, and negative symptoms) rather than treating the entire illness with a single medication. Clinicians would first treat the psychotic symptoms with available antipsychotics and then focus on treating a person's cognitive and negative symptoms. Pharmacologic treatments for cognitive dysfunction and negative symptoms are still under development, and the focus on molecular targets may lead to the discovery and development of new compounds.

Drug names: atomoxetine (Strattera), atropine (Atropen and others), clozapine (Clozaril, FazaClo, and others), ketamine (Ketalar), olanzapine (Zyprexa), scopolamine (Transderm Scop), tolcapone (Tasmar).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, atomoxetine, atropine, clozapine, ketamine, olanzapine, physostigmine, scopolamine, tolcapone, D-cycloserine, glycine, phencyclidine, tandospirone, and xanomeline are not approved by the U.S. Food and Drug Administration for the treatment of cognition in schizophrenia.

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