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Molecular Targets for Treating Cognitive Dysfunction in Schizophrenia

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Cognitive impairment is a core feature of schizophrenia as deficits are present in the majority of patients, frequently precede the onset of other positive symptoms, persist even with successful treatment of positive symptoms, and account for a significant portion of functional impairment in schizophrenia. While the atypical antipsychotics have produced incremental improvements in the cognitive function of patients with schizophrenia, overall treatment remains inadequate. In recent years, there has been an increased interest in developing novel strategies for treating the cognitive deficits in schizophrenia, focusing on ameliorating impairments in working memory, attention, and social cognition. Here we review various molecular targets that are actively being explored for potential drug discovery efforts in schizophrenia and cognition. These molecular targets include dopamine receptors in the prefrontal cortex, nicotinic and muscarinic acetylcholine receptors, the glutamatergic excitatory synapse, various serotonin receptors, and the γ-aminobutyric acid (GABA) system.

Key words: serotonin/dopamine/glutamate/NMDA/acetylcholine/GABA

Introduction

Schizophrenia is characterized by positive symptoms such as delusions and hallucinations, negative symptoms such as avolition and flat affect, and cognitive impairments. Although Kraepelin,[1] with his term "dementia praecox," characterized the relationship between cognitive deficits and schizophrenia nearly a century ago, effective treatments for these deficits have not been developed. Cognitive dysfunction is estimated to occur in 75%–85% of patients with schizophrenia,[2] often precedes the onset of other symptoms,[2] and persists even after other symptoms have been effectively treated.[3] Indeed, a meta-analysis of cognitive deficits suggested that indices of cognitive deficits are much better predictors of functional outcome than indices from any other symptom domain.[4] Furthermore, the severity of cognitive deficits is predictive of poorer medication compliance,[5] overall treatment adherence,[6] and increased tendency for relapse in first-episode patients.[7]

Until recently, antipsychotic drug development in schizophrenia has focused mainly on developing drugs that reduce the positive symptoms of schizophrenia,[8] and indeed, all the current medications appear to be similar in efficacy for reducing positive symptoms in typical patients with schizophrenia.[9,10] In a recent meta-analysis, patients treated with typical antipsychotics were actually shown to have small but detectable improvements in several cognitive domains[11]; however, due to extrapyramidal side effects, many patients are also treated with anticholinergic agents that are well known to impair memory[12] and global cognitive ability.[13] In addition, there is some evidence for the superiority of atypical antipsychotics, such as olanzapine and risperidone, over typicals in improving cognitive performance,[14–16] though the benefits are relatively small and have not been consistently reproduced.[17] Overall, the widespread use of the atypical antipsychotics has likely offered some cognitive benefit for patients with schizophrenia,[18] though significant deficits persist, suggesting a need for directive treatments for enhancing cognition.

Due to the continued need for improved treatment of the cognitive impairments in schizophrenia, Wayne Fenton spearheaded the National Institutes of Mental Health's joint academic and industry initiative termed MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) to facilitate the development of better treatments targeted at cognition.[19] An initial MATRICS conference (http://www.matrics.ucla.edu) identified 7 primary cognitive domains that are crucial for developing targets for the treatment of cognition in schizophrenia. These domains included working memory, speed of processing, verbal learning and memory, attention and vigilance, reasoning and problem solving, visual learning and memory, and social cognition.[20–22] An additional MATRICS conference (http://www.matrics.ucla.edu) identified pharmacologic strategies that hold promise for the treatment of impaired cognition in schizophrenia.

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The primary molecular targets identified included dopamine receptors in the prefrontal cortex, nicotinic and muscarinic acetylcholine receptors, the glutamatergic excitatory synapse, various serotonin receptors, and the γ-aminobutyric acid (GABA) system. Below, we review many of the molecular targets being studied for potential drug development strategies aimed at enhancing cognition, both generally and specifically in schizophrenia (table 1).

Cholinergic Targets

Acetylcholine is known to play an important role not only in motor function but also in various domains of cognition, particularly attention, learning, and memory.[23] Indeed, cholinergic dysfunction has been shown to be central to the pathophysiology of Alzheimer's disease and has also been postulated to contribute to the cognitive deficits of various neuropsychiatric disorders, including schizophrenia.[23] The basal cholinergic complex sends widely diffuse afferents through 2 projections: the septohippocampal and the nucleus basalis of Meynart cortical pathways.[24] The septohippocampal pathway is important in working memory processes through hippocampal storage of intermediate-term memory,[25,26] whereas the nucleus basalis of Meynart cortical pathway is involved in reference memory through long-term information storage in the neocortex.[27,28] Additionally, a role for acetylcholine in the processes of attention has been demonstrated in rats and monkeys.[29] Pharmacologically, anticholinergic drugs, like scopolamine, produce learning impairments in healthy subjects similar to those of persons with dementia,[30] while cholinomimetic drugs, like physostigmine, can significantly enhance the memory functions of healthy individuals.[30,31]

Although the degeneration of cholinergic neurons in the basal forebrain and the associated loss of cerebral neurotransmission that is seen in Alzheimer's disease are absent in schizophrenia,[32,33] there is evidence of decreased nicotinic[34] and muscarinic[35] acetylcholine receptors in the cortex and hippocampus of individuals with schizophrenia. Interestingly, in patients with schizophrenia, decreased activity of choline acetyltransferase, a biosynthetic enzyme for acetylcholine production, was correlated with poorer cognitive functioning as measured by the Clinical Dementia Rating.[33] In addition, some of the atypical antipsychotics, but not typical antipsychotics, can increase the release of acetylcholine in the prefrontal cortex, possibly contributing to their modest enhancement of cognition in schizophrenia.[36] Thus, various targets within the cholinergic system are being investigated as potential enhancers of cognition in schizophrenia.

Cholinesterases

Cholinesterase inhibitors, such as donepezil and rivastigmine, are currently the main pharmacologic approach to

Table 1. Molecular Targets for Cognitive Enhancement in Schizophrenia

Molecular Target	Example Compound	Clinical Evidence
D_1 agonists[a]	Dihydrexidine	Positive proof-of-concept trials
D_4 antagonists	Sonepiprazole	Ineffective in acute schizophrenia
D_4 agonists	A-412997	n/a
COMT inhibitors	Tolcapone	Improved cognition in Parkinson's disease
5-HT_{2A} antagonists	M100907	Modest efficacy in acute schizophrenia
5-HT_{1A} agonists	Tandospirone	Mixed results
5-HT_{1A} antagonists	WAY100635	n/a
5-HT_4 agonists	Tegaserod	Recently withdrawn from market in IBS[b]
5-HT_6 antagonists	SB-271046	n/a
5-HT_7 agonists	No selective ligands	n/a
Cholinesterase inhibitors	Donepezil	Multiple trials, mixed results
Nicotinic α_7 agonists	DMXB-A	Positive proof-of-concept trials
Nicotinic $\alpha_4\beta_2$ agonists	RJR2403	n/a
M_1 agonists	NDMC (nonselective)	Positive effects with nonselective agonists
M_4 agonists	No selective ligands	n/a
M_5 antagonists	No selective ligands	n/a
NMDA enhancers	Glycine	Multiple small trials, mostly positive
GlyT inhibitors	Org-24598	Positive proof-of-concept trials
Ampakines	CX-516	Mixed proof-of-concept trials
mGluR2/3 agonists	Unknown	Positive proof-of-concept trial reported
mGluR5 agonists	CDPPB	n/a
α_2-adrenergic antagonists	Guanfacine	Positive small trials
$GABA_A$ (α_2) agonists	TPA023	Single positive proof-of-concept trial
$GABA_A$ (α_5) antagonists	L-655708	n/a
Sigma agonists	No selective ligands	n/a

Note: D, dopamine; n/a, clinical evidence not available to date; COMT, catechol-*O*-methyltransferase; 5-HT, serotonin; IBS, irritable bowel syndrome; DMXB-A, 3-2,4-dimethoxybenzylidene anabaseine; M, muscarinic; NMDA, *N*-methyl-D-aspartate; GlyT, glycine transporter; mGluR, metabotropic glutamate receptor; GABA, γ-aminobutyric acid.

[a]The term "agonist" is used here to refer to agonists, partial agonists, and positive allosteric modulators.

[b]withdrawn due to increase in adverse cardiovascular events.

the treatment of Alzheimer's disease and have been shown to slow the cognitive decline in this neurodegenerative disease.[37] As such, it has been proposed that cholinesterase inhibitors may also be useful in the treatment of the cognitive dysfunction in schizophrenia.[38] Acetylcholinesterase and butyrylcholinesterase are present in a wide variety of tissues and are broadly distributed in the brain. Inhibition of cholinesterases increases the synaptic concentration of acetylcholine, thereby enhancing and prolonging the action of acetylcholine on both muscarinic and nicotinic receptors. Therefore, cholinesterase inhibitors act as indirect cholinergic agonists at muscarinic and nicotinic receptors.

Following the administration of atypical antipsychotic treatment, cholinesterase inhibitors can increase the concentration of acetylcholine in the medial prefrontal cortex by 2- to 3-fold[36] and have been demonstrated to produce some functional normalization of brain activity during verbal fluency task performance of schizophrenic patients characterized by a significant increase in frontal lobe and cingulate activity on functional magnetic resonance imaging (fMRI).[39] As such, in recent years there have been multiple small randomized controlled trials of cholinesterase inhibitors in patients with schizophrenia, though results have been disappointing and inconsistent.[40] It has been suggested that the lack of consistent effects of cholinesterase inhibitors may be due to the high rate of cigarette smoking among patients with schizophrenia[41] and subsequent desensitization of nicotinic receptors,[42] thus rendering increased acetylcholine levels ineffective.[43] Indeed, galantamine, an acetylcholinesterase inhibitor that is also an allosteric potentiator of α_7 nicotinic receptors,[44,45] does not cause α_7 receptor desensitization and has been shown to enhance cognitive functioning of schizophrenic patients in a 4-week double-blind placebo controlled trial.[46] Interestingly, galantamine produced cognitive enhancement in schizophrenic patients despite the fact that all the patients smoked at least 10 cigarettes per day.[46] Unfortunately, despite these initial positive findings, subsequent results with galantamine have been mixed.[47–49] Thus, while pure cholinesterase inhibitors may be of minimal benefit for enhancing cognition in patients with schizophrenia, possibly due to desensitization of their α_7 nicotinic receptors from cigarette smoking, further study may be warranted with combined acetylcholinesterase inhibitors and allosteric potentiators of the nicotinic receptor in schizophrenia. However, it is likely that selective agents at various nicotinic and muscarinic receptors may be a more effective approach to developing drugs for treatment of the cognitive impairment in schizophrenia.

Nicotinic Receptors

It is well known that the smoking rates in individuals with schizophrenia are significantly higher than in the general population, and some have suggested that these individuals may be "self-medicating" with nicotine.[50,51] Indeed, nicotine administration has been shown to improve various measures of cognition that may ease some of the side effects of antipsychotic medications.[51] For example, in patients with schizophrenia, a nicotine transdermal patch could dose dependently reverse haloperidol-induced impairments in working memory, attention, and reaction time[52] and has been shown to reduce haloperidol-induced bradykinesia and rigidity compared with a placebo patch.[53] However, other studies have been mixed.[54] Interestingly, in one study,[55] some of the modest effects of cigarette smoking on clinical and cognitive outcome measures could also be improved by smoking denicotinized cigarettes, suggesting that nonnicotine components of cigarette smoke may also contribute.[55] Overall, while research on nicotinic treatment of individuals with schizophrenia has shown that, in single administrations, nicotine improves some aspects of cognition, additional administrations are not effective due to rapid desensitization of nicotinic receptors.[42] Thus, considerable research is exploring the potential use of nicotinic agents, particularly partial agonists and allosteric modulators at various nicotinic receptor subunits that would be less likely to cause rapid receptor desensitization.

Nicotinic acetylcholine receptors are ionotropic receptors with a pentameric structure composed of alpha (α_2 to α_9) and beta (β_2 to β_4) subunits and are expressed at high levels in the hippocampus, cortex, striatum, and thalamus.[34,56] The 2 most prevalent nicotinic receptors are the $\alpha_4\beta_2$, which is a high-affinity receptor, and the α_7, which is a low-affinity nicotinic receptor, both of which have been shown to have reduced numbers in patients with schizophrenia.[34,56] In addition, functional polymorphisms exist in the promoter region of the α_7 receptor that have shown genetic linkage in schizophrenia.[57,58]

The α_7 nicotinic receptor subtype is a highly studied target for the development of drugs for cognitive enhancement. Studies in rodents have shown that antagonists at the α_7 nicotinic receptor induce sensory gating deficits similar to those seen in schizophrenia,[59] a hippocampal phenomenon manifested as an inability to attend appropriately to sensory stimuli.[60] Sensory gating deficits may strongly impact cognitive performance, and it has been shown that smoking transiently normalizes these sensory gating deficits.[60] In addition, agonists at α_7 receptors such as 3-2,4-dimethoxybenzylidene anabaseine (DMXB-A) can normalize the auditory gating deficits in rodents.[61] Moreover, DMXB-A had a positive effect on a cognitive battery in a small proof-of-concept trial in humans,[62] and additional clinical trials of α_7 receptor agonists are underway. However, there is concern that long-term use of α_7 agonists may induce the desensitization of nicotinic receptors, leading to a limited duration of efficacy.[63] Thus, further development of α_7 receptor partial agonists (eg, GTS-21) and allosteric potentiators (eg, galantamine) that induce minimal receptor desensitization is warranted.

In addition to α_7 receptors, it has been suggested that $\alpha_4\beta_2$ nicotinic receptors are involved in cognition.[64] Indeed, $\alpha_4\beta_2$ receptors are considered to represent more than 90% of the high-affinity nicotine-binding sites in the rat brain,[65] and decreased levels of $\alpha_4\beta_2$ receptor binding have been found in the hippocampus of patients with schizophrenia.[56] Furthermore, agonists of $\alpha_4\beta_2$ receptors, such as RJR2403 and SIB-1553A, can produce a significant and long-lasting improvement of memory in rats and monkeys.[66–68] Additionally, $\alpha_4\beta_2$ agonists have been shown to stimulate the release of dopamine, norepinephrine, and acetylcholine in the hippocampus and frontal cortex in rats.[66] Thus, nicotinic $\alpha_4\beta_2$ receptor agonists may be of therapeutic benefit for the treatment of the cognitive deficits in schizophrenia by several mechanisms. In addition to α_7 and $\alpha_4\beta_2$ receptors, other nicotinic receptors, such as α_3- and α_6-containing receptors, may be involved in cognitive performance; however, studies are limited due to the lack of selective agonists and antagonists for these receptors.

Muscarinic Receptors

In addition to the ionotropic nicotinic receptors, numerous studies have implicated metabotropic muscarinic acetylcholine receptors in schizophrenia. Muscarinic receptors are G protein–coupled receptors[69] found widely throughout the central nervous system on both cholinergic and noncholinergic cells where they function as both autoreceptors and heteroreceptors.[70–72] Of the 5 genetically distinct subtypes of muscarinic receptors (M_1–M_5), the M_1 receptor has been most closely linked to cognition and schizophrenia.[73] Indeed, the M_1 receptor subtype is the most abundant of the muscarinic receptors in forebrain and hippocampus,[74,75] brain regions crucial to normal cognitive functions. In addition, decreased M_1 receptor binding has been reported in postmortem studies of the prefrontal cortex, hippocampus, and striatum from patients with schizophrenia,[76–78] that is, importantly, not due to chronic antipsychotic treatment.[35,77,79] Interestingly, M_1 receptor–deficient mice demonstrate deficits in working memory and remote reference memory indicative of impaired hippocampal-cortical interactions.[80] Together, these results suggest that alterations in central M_1 receptors may have a role in the pathophysiology of schizophrenia and that M_1 receptor agonists may be beneficial in treating schizophrenia, particularly the cognitive impairments.[73]

Action at M_1 receptors has been proposed to be a major contributor to the cognition-enhancing effects of clozapine,[81] despite the fact that clozapine is an exceedingly weak partial agonist at M_1 and other muscarinic receptors.[73,82] Thus, attention has focused on various clozapine metabolites including clozapine-*N*-oxide and *N*-desmethylclozapine (NDMC). Clozapine-*N*-oxide is inactive while NDMC has actions at many receptors (http://pdsp.med.unc.edu/pdsp.php).[82] Interestingly, NDMC is the major active metabolic of clozapine and has been reported to be a potent M_1 agonist that preferentially binds to M_1 receptors vs clozapine,[83] although more comprehensive studies fail to demonstrate selectivity of NDMC for M_1 receptors.[84] In addition, NDMC has high affinities for 5-HT_{2A} and 5-HT_{2C} receptors and is a partial agonist at D_2, D_3 receptors[85,86] and δ-opioid receptors,[87] suggesting that this metabolite of clozapine may have antipsychotic and cognition-enhancing properties via a number of mechanisms. Furthermore, NDMC, but not clozapine, increases release of dopamine and acetylcholine in the prefrontal cortex and the hippocampus[88] and potentiates NMDA receptor activity in the hippocampus.[83] Thus, the cognitive enhancement observed with clozapine could actually be due to its metabolite NDMC via an uncertain mechanism.

Indeed, NDMC (ACP-104) and other M_1 receptor agonists are in clinical trials as potential treatments of the cognitive dysfunction in schizophrenia. Xanomeline, a nonselective M_1 and M_4 muscarinic agonist with potent actions at a variety of additional nonmuscarinic receptors including 5-HT_{1A} and 5-HT_{2A} receptors,[89] improved cognition and psychotic-like symptoms in Alzheimer's disease.[90] In addition, monotherapy with xanomeline resulted in an improvement of positive symptoms and cognitive function in 20 subjects with schizophrenia[91] but was discontinued due to poor tolerability.[92] The relatively nonselective actions of xanomeline and NMDC at a number of receptors (http://pdsp.med.unc.edu/pdsp.php) should engender caution among schizophrenia researchers for embracing positive data from xanomeline and NMDC studies as being specifically indicative of a role for M_1 receptors in schizophrenia.

Overall, evidence suggests that M_1 receptor agonists could be useful in treating various symptom domains in schizophrenia, though the roles of the other muscarinic receptor subtypes are less clear. M_5 receptors, for example, may be relevant to schizophrenia as they are located in the brainstem and midbrain, where they have an effect on dopamine release.[93] Indeed, xanomeline is also an antagonist at M_5 receptors, suggesting that blockade of M_5 may be involved in the benefits seen with xanomeline.[94] In addition, M_4 receptor knockout mice have impairments of cognitive performance and elevated levels of dopamine in the nucleus accumbens, suggesting a potential role for M_4 receptor agonists in treating both the positive and cognitive symptoms of schizophrenia.[95,96] As selective agonists at muscarinic receptor subtypes have been difficult to develop, positive allosteric modulators are also being explored as potential therapeutic agents.

Glutaminergic Targets

Glutamate is the primary excitatory neurotransmitter for approximately 60% of the neurons in the mammalian brain, including all cortical pyramidal neurons,[97] and

plays a principal role in modulating long-term potentiation, a likely key cellular mechanism for learning and memory.[98,99] Glutamate mediates fast excitatory postsynaptic potentials by acting on 3 ionotropic receptors, which are differentiated based upon sensitivity to the synthetic glutamate derivatives *N*-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate.[100] In addition, glutamate exerts slower modulatory effects by acting on various G protein–coupled metabotropic glutamate receptors (mGluRs).[101] For example, mGluR2 and mGluR3 receptors modulate the release of glutamate, whereas the mGluR5 receptor potentiates the duration of NMDA receptor–dependent excitatory postsynaptic potentials.[102]

It has been hypothesized for decades that some deficiency in NMDA function might play a role in the pathophysiology of schizophrenia.[103] Since the 1950s, the NMDA receptor antagonists phencyclidine (PCP) and ketamine were known to produce a large range of schizophrenia-like symptoms including psychotic symptoms, negative symptoms, and cognitive dysfunction,[103–105] and it has been suggested that augmenting NMDA receptor activity may have therapeutic potential in schizophrenia.[100] Indeed, some of the atypical antipsychotics, but not typical antipsychotics, have been shown in preclinical models to reverse the effects of ketamine and PCP,[106–109] presumably through indirect activation of NMDA receptors mediated by other neurotransmitter systems.[83] It is also important to note that a competing hypothesis suggests that a hyperactivity of glutamatergic neurotransmission is involved in the psychopathology of schizophrenia, leading to seemingly contradictory pharmacologic approaches being explored.[100] Indeed, glutamatergic excitotoxicity is thought to be a factor in the neurodegeneration of Alzheimer's disease[110] and a weak NMDA receptor antagonist, memantine, has shown efficacy in slowing cognitive decline in moderate to advanced Alzheimer's disease.[111] Thus, the glutamate system, especially its NMDA-dependent components, is complex, and while small increases in NMDA-dependent glutamate neurotransmission might be cognitively enhancing, too much activation may result in neurodegeneration. Fortunately, the glutamatergic excitatory synapse offers multiple targets for drug development to provide the precise level of enhancement to improve cognition without excitotoxicity. Thus, we briefly review below various approaches being explored for modulating NMDA receptor neurotransmission and discuss approaches aimed at other glutamatergic mediators.

NMDA Receptors

NMDA glutamate receptors are ligand-gated ion channels with a primary glutamate-binding site and an allosteric glycine-binding site.[100] Interestingly, the opening of the NMDA channel appears to require both glutamate and glycine binding, with glycine binding affecting channel open time and desensitization rate but not inducing channel opening itself.[100] In addition, NMDA receptor activity can be allosterically modulated by multiple other substances, including Mg^{2+}, polyamines, and protons.[112] Thus, while direct agonists of the glutamate-binding site of the NMDA receptor may not be clinically feasible due to the risk of excess excitation and neurotoxicity, the allosteric sites on the NMDA receptor complex, particularly the glycine-binding site, are promising targets for drug development. Indeed, chronic treatment of rodents with glycine has not been found to induce excitotoxicity.[113,114]

Compounds that target the glycine site of the NMDA receptor complex have been studied in multiple small clinical trials. These include glycine[115] and D-serine,[116] which are endogenous agonists at the glycine site of the NMDA receptor complex; D-alanine; and D-cycloserine, an antituberculosis drug that also binds to the glycine modulatory site where it functions as a partial agonist.[117] In most of these studies, the test compound was administered along with either a typical or atypical antipsychotic, and there appears to be significant effects at reducing negative symptoms and cognitive impairment in patients with schizophrenia.[118] Of the 4 agents, D-cycloserine has been the least efficacious, likely due to it being a partial agonist that acts as an antagonist at high doses. Interestingly, when used concurrently with clozapine, glycine[119] and D-serine[120] have been reported to be ineffective while D-cycloserine seemed to worsen symptoms,[121] possibly because clozapine may already enhance glycine and glutamate neurotransmission. Overall, agonists at the glycine allosteric site of the NMDA glutamate receptor hold promise in the treatment of the negative and cognitive symptoms of schizophrenia, possibly as an augmentation of currently existing antipsychotics. A potential limitation of targeting the glycine modulatory site is that the glycine site is probably half-saturated during physiologic conditions, suggesting that treatments targeting the glycine site would theoretically only be able to effectively double NMDA neurotransmission.[118] In addition, both glycine and D-serine must be given at gram-level doses to significantly elevate central nervous system levels, and attempts to modify glycine or D-serine to produce synthetic glycine-site agonists, have, thus far, been unsuccessful. Thus, indirect approaches to activate NMDA receptors are being explored, such as increasing extracellular glycine and glutamate and by modulating AMPA receptors and mGluRs.

Glycine Transporters

An indirect approach being explored to boost NMDA activity via the glycine allosteric site is to increase synaptic glycine by inhibiting the glycine transporter. The glycine transporters, GlyT1 and GlyT2, have been identified on both neuronal and glial cells in the central nervous

system, where they are suggested to control the extracellular concentration of glycine.[122] Thus, blockade of glycine transporters is predicted to increase extracellular glycine and thus enhance NMDA receptor neurotransmission. Indeed, preclinical data suggest that inhibition of glycine reuptake represents a feasible approach to enhance NMDA receptor activity and possibly be therapeutic in schizophrenia.[100] For example, selective, high-affinity inhibitors of the glycine transporter, including Org-24598, N-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl] sarcosine, and SSR-504734, have been found to reverse PCP-induced hyperactivity and dopaminergic hyperreactivity in rodents.[123,124] Furthermore, the glycine transport inhibitor glycyldodecylamide attenuated PCP-induced hyperactivity more potently than administration of glycine.[125,126]

Clinical trials to date, however, have only studied the low-potency glycine transport inhibitor sarcosine (*N*-methyl glycine). In a clinical trial of sarcosine added to the stable antipsychotic regimen of patient with schizophrenia, there was a highly significant reduction in negative symptoms, along with smaller but significant reductions in positive and cognitive symptoms.[127] Interestingly, a subsequent study with patients on clozapine found no improvement of symptoms with the addition of sarcosine, a result similar to studies with the NMDA glycine site agonists.[128] These results strongly suggest a role of glycine transport inhibitors in the treatment of schizophrenia, though results of trials with selective, high-potency inhibitors are anticipated.

AMPA/Kainate Receptors

Another glutamatergic approach to drug development for cognitive enhancement in schizophrenia has been the development of compounds that stimulate AMPA and kainate glutamate receptors. AMPA and kainate receptors mediate the majority of the fast glutamatergic signaling in the brain, and AMPA receptors work heavily in concert with NMDA receptors.[100] AMPA receptors provide the primary depolarization necessary to activate NMDA receptors, while NMDA receptors are required for proper incorporation of AMPA receptors into the postsynaptic membrane, a process involved in synaptic plasticity.[129] Thus, activation of AMPA receptors is likely critically important for learning and memory; however, direct AMPA agonists are unlikely to be therapeutically useful as AMPA receptors rapidly desensitize after stimulation.[130]

In an attempt to avoid desensitization of AMPA receptors, allosteric potentiators of AMPA receptor function, a class of compounds termed ampakines, are being studied as potential treatments for enhancing cognition in schizophrenia.[131,132] Indeed, ampakines have been shown to enhance glutamatergic transmission and facilitate long-term potentiation in rodents.[133,134] Furthermore, ampakines improve performance in rodents on a variety of memory tasks including spatial mazes[135,136] and learned fear[137] and have been shown to be effective in reducing age-associated memory deficits in rats.[138] In a clinical trial of schizophrenia patients on clozapine, coadministration of the ampakine CX-516 yielded significant improvements in memory and attention;[139] however, a trial of CX-516 as monotherapy in schizophrenia showed no clear beneficial effects.[140] Importantly, higher potency ampakines are currently under clinical development as both monotherapy for schizophrenia and adjunctive treatment for cognitive dysfunction, though results of trials are not yet available. A higher potency ampakine, farampator, has been tested in healthy elderly volunteers and improved short-term memory but appeared to impair episodic memory,[141] and thus, it remains unclear if modulation of AMPA receptors has therapeutic value in the treatment of the cognitive dysfunction in schizophrenia although this is a highly active area of current research.

Metabotropic Glutamate Receptors

Agents acting at mGluRs, which serve to regulate glutamatergic neurotransmission both pre- and postsynaptically, are currently in preclinical development for treatment of the cognitive dysfunction in schizophrenia. There are 8 subtypes of mGluRs (mGluR1–8) which are categorized into 3 groups according to their second messenger-coupling and ligand-binding profiles with group I receptors (mGluR1 and mGluR5) primarily being studied for cognitive enhancement in schizophrenia.[102] Group I receptors, particularly mGluR5, function predominantly to potentiate both presynaptic glutamate release and postsynaptic NMDA neurotransmission,[142] and mGluR5 receptors show significant colocalization with NMDA receptors in cortical pyramidal neurons.[143] Together, these findings suggest that mGluR5 agonism may enhance NMDA activity and improve memory and cognition.[142] Indeed, selective mGluR5 agonists were found to inhibit PCP-induced dopamine release in the rodent prefrontal cortex.[144] Direct mGluR5 agonists, however, are likely to induce receptor desensitization limiting their therapeutic usefulness. Thus, selective allosteric potentiators of mGluRs have recently been developed and hold promise as therapeutic agents.[145,146] Indeed, preliminary positive results with an mGluR2/3 agonist in phase II trials have been reported (http://www.prnewswire.com/cgi-bin/micro_stories.pl?ACCT=916306&TICK=LLY&STORY=/www/story/12-07-2006/0004487009&EDATE=Dec+7,+2006).

Dopaminergic Targets

Dopamine projections to the prefrontal cortex comprising the mesocortical dopamine system are essential for normal cognition.[147,148] Thus, it has been hypothesized

that decreased dopaminergic neurotransmission in the prefrontal cortex contributes to the cognitive deficits observed in schizophrenia, especially those related to executive functions and working memory.[149–151] Indeed, postmortem and in vivo imaging studies have linked prefrontal dopamine dysfunction to cognitive impairment,[151,152] and various studies have demonstrated that direct and indirect dopamine agonists can improve prefrontal cortex cognitive functions in humans.[153,154] However, it seems that precise regulation of prefrontal dopaminergic tone is essential as, in addition to insufficient dopamine, excessive prefrontal dopamine (eg, resulting from acute stress) may be deleterious to cognition.[155–157] Thus, dopamine function in the prefrontal cortex seems to follow an "inverted-U" dose-response curve whereby increases or decreases from an optimal level result in cognitive impairment.[158] Additionally, indirect dopamine agonists could potentially exacerbate psychosis by increasing neurotransmission at mesolimbic dopamine D_2 receptors.

D_1 Receptors

Dopamine D_1 receptors are expressed at high levels on the distal dendrites of pyramidal neurons in the prefrontal cortex that are thought to be involved in working memory processes.[158,159] Indeed, evidence suggests an important role of dopamine D_1 receptors in the cognitive dysfunction of schizophrenia.[138] For example, there is a decreased level of D_1 receptor–like binding in the prefrontal cortex of drug-naive patients with schizophrenia as measured with positron emission tomography imaging, and this decrease was found to be correlated with the severity of negative symptoms and cognitive dysfunction but not with the severity of positive symptoms.[160] In addition, in nonhuman primates, chronic blockade of D_2 receptors results in a downregulation of D_1 receptors in the prefrontal cortex and consequently produces severe impairments in working memory.[161] This downregulation of D_1 receptors may explain why long-term treatment with typical antipsychotics can contribute to the cognitive dysfunction in schizophrenia. Thus, significant efforts are underway to examine the possible role of D_1 receptor agonists in treating cognitive dysfunction in schizophrenia. Indeed, low doses of selective D_1 agonists, such as dihydrexidine, A77636, and SKF81297, have cognition-enhancing actions in nonhuman primates,[162–164] and short-term administration of the D_1 selective agonist, ABT-431, reversed the cognitive deficits in monkeys treated chronically with a D_2 receptor antagonist.[161]

Although novel compounds that, directly or indirectly, stimulate D_1 receptors may be of immense value in treating cognitive deficits in schizophrenia, several potential pitfalls may need to be overcome. First, D_1 receptor activity follows the "inverted-U" dose-response curve, where either too little or too much D_1 stimulation impairs working memory.[158] In addition, chronic treatment with a D_1 agonist may actually lead to the downregulation of D_1 receptors which could, potentially, worsen cognition in the long term. Thus, an optimized level of D_1 receptor activation at the apex of the "inverted-U" may be required to obtain maximal cognitive benefits,[157] which may be accomplished by partial agonists or an intermittent pattern of administration.[161,165] An additional obstacle is the powerful hypotensive effects of direct-acting D_1 agonists on peripheral D_1 receptors,[166] which may necessitate the use of indirect D_1-activating agents such as catechol-*O*-methyltransferase (COMT) inhibitors (see below).

D_4 Receptors

The high affinity of clozapine for dopamine D_4 receptors led to speculation that D_4 receptors may be clozapine's "magic receptor."[167] Clinical trials of selective D_4 antagonists, however, have not demonstrated any appreciable efficacy in the treatment of acute schizophrenia,[168–170] though it is possible that D_4 receptor blockade in collaboration with action at other neurotransmitter receptors may be clinically beneficial. Indeed, studies of the physiological roles for the D_4 receptor are finding that D_4 receptors may play an important role in impulsivity and working memory.[171]

The mechanism by which D_4 blockade could improve cognition is not fully known,[172] though D_4 receptors are present on both pyramidal neurons and GABA-producing interneurons in the prefrontal cortex and hippocampus,[173] areas important for cognitive function. Studies have demonstrated that activation of D_4 receptors decreases NMDA receptor activity in the hippocampus[174] and inhibits glutamatergic signaling in the prefrontal cortex.[175] Additionally, D_4 receptor knockout mice show enhanced activity of cortical pyramidal neurons, an effect mimicked in wild-type mice by administration of the D_4 antagonist PNU-101387G.[175] Together, these results suggest that D_4 antagonism may be a valuable approach to improve cognition in schizophrenia. Indeed, the D_4 antagonist NDG96-1 was reported to reverse PCP-induced deficits in object retrieval tasks in monkeys,[172] and another D_4 antagonist, PNU-101387G, reversed deficits in the delayed response task induced by the pharmacologic stressor FG7142 (a benzodiazepine inverse agonist).[176] Interestingly, PCP-induced cognitive deficits are exacerbated by haloperidol, suggesting that strong blockade of other dopamine receptors may counter the beneficial effects of D_4 blockade on cognitive functioning.[172]

Seemingly contradictory evidence also suggests that D_4 receptor agonists may improve cognitive function. For example, the selective D_4 agonist A-412997 showed dose-dependent improvement in social recognition in rats, a model of short-term memory,[177] and the D_4

agonist PD168077 was shown to facilitate memory consolidation of an inhibitory avoidance learned response in mice.[178] These effects have been hypothesized to be due to D_4 receptor modulation of inhibitory GABAergic signaling in the prefrontal cortex.[179] Indeed, the D_4 agonist PD168077 reduces $GABA_A$ inhibitory currents in pyramidal neurons, which could be blocked by the D_4 antagonist L-745870 as well as clozapine.[179] Thus, in contrast to D_4 antagonist–induced enhancement of NMDA currents in the hippocampus, D_4 agonists may suppress $GABA_A$ inhibitory currents in the prefrontal cortex and thereby indirectly enhance cortical excitability. Taken together, D_4 receptor–selective agents may be valuable in the treatment of the cognitive deficits in schizophrenia, though a balance between D_4 receptor modulation of prefrontal $GABA_A$ and hippocampal NMDA receptors may be necessary.

Catechol-O-methyltransferase

COMT is a postsynaptic enzyme that methylates and thereby deactivates synaptically released catecholamines, particularly dopamine.[180] Historically, monoamine oxidase was considered the primary enzyme for the initial deactivation of synaptic dopamine,[181] though mounting evidence suggests that COMT may be especially important for the breakdown of dopamine, particularly in the prefrontal cortex.[182] For example, COMT knockout mice show increased baseline levels of dopamine, but not other catecholamines such as norepinephrine, specifically in the frontal cortex.[183] In addition, the COMT knockout mice also showed enhanced memory performance,[183] suggesting a potential role of COMT inhibition in improving cognition. Indeed, a selective, reversible inhibitor of COMT, tolcapone, has been reported to improve working memory in rodents[184] and has been shown to improve cognitive dysfunction in patients with advanced Parkinson's disease,[185] though use is limited due to a risk of liver failure.[186] Other COMT inhibitors are currently being investigated for treatment of the cognitive dysfunction in schizophrenia.

Interestingly, a common single nucleotide polymorphism in the gene encoding COMT, Val158Met, results in the transcription of a variant of the COMT enzyme with approximately 40% less enzymatic activity in humans.[187] The reduced COMT enzymatic activity associated with the Met variant presumably results in greater availability of dopamine in the prefrontal cortex and, thus, may improve cognition, hypotheses supported by findings from the COMT knockout mice,[183] and an fMRI study in humans.[188] Furthermore, the COMT locus at chromosome 22q11 has been identified as a susceptibility locus for schizophrenia in several linkage studies[189,190] and 2 meta-analyzes,[189,191] though this remains controversial.[192–194] However, accumulating evidence predicts that patients with schizophrenia who have the Met allele may have improved cognitive response to clozapine.[195] Interestingly, a recent proof-of-concept experiment in normal human subjects treated with tolcapone demonstrated significant improvements on measures of executive function and verbal episodic memory in individuals with a Val/Val genotype but a diminished performance of individuals with the Met/Met genotype.[196] Thus, overall, the potential of pharmacologic inhibition of COMT in the long-term treatment of the cognitive dysfunction in schizophrenia remains to be determined.

Serotonergic Targets

5-HT_{2A} Receptors

5-HT_{2A} receptors are particularly abundant in the pyramidal neurons from cortical layer V,[197] where they have been described to colocalize with NMDA glutamate receptors,[198,199] suggesting a role in modulating cognitive functions. Indeed, studies have demonstrated that 5-HT_{2A} receptors interact with postsynaptic density protein 95, a protein involved in anchoring NMDA receptors to postsynaptic densities,[200] and it has been suggested that activation of 5-HT_{2A} receptors increases the release of glutamate onto pyramidal cells.[201] Interestingly, the selective 5-HT_{2A} receptor antagonist M100907 blocked the cognition-impairing effects of MK-801, an NMDA receptor antagonist.[202,203] Similar findings have been reported for another 5-HT_{2A} antagonist AC-90179.[204] Taken together, these studies suggest an intimate association between NMDA and 5-HT_{2A} receptors and imply that drugs with potent 5-HT_{2A} antagonistic actions may prove beneficial at improving cognition in schizophrenia, perhaps by normalizing NMDA receptor functioning.[203]

In addition, 5-HT_{2A} receptors are located on dopaminergic neurons in the ventral tegmental area,[205] where they may modulate dopamine neuronal activity.[206] Indeed, it is likely that a predominant role of 5-HT_{2A} receptors in antipsychotic action is to modulate dopaminergic tone, particularly along the mesocortical pathway.[206–208] For example, clozapine, olanzapine, and ziprasidone, but not haloperidol or risperidone, can preferentially augment dopamine and norepinephrine release in the prefrontal cortex relative to the subcortical areas.[209] In rats, however, repeated administration of the selective 5-HT_{2A} antagonist M100907 can alter the activity of midbrain dopamine neurons in rats, though there is disagreement as to whether cortical dopamine levels are potentiated[210] or inhibited.[211] Thus, it has been hypothesized that the ultimate effect of 5-HT_{2A} antagonists on dopaminergic neurotransmission might be to stabilize it.[208,212]

Clinical studies with selective 5-HT_{2A} receptor compounds have also demonstrated a role of 5-HT_{2A} receptors in cognitive functioning in schizophrenia. For example, in a study of 30 hospitalized patients with schizophrenia, administration of mianserin, a 5-$HT_{2A/2C}$ and α_2-adrenergic

antagonist, improved scores on the Automated Neuropsychological Assessment Metrics at 4 weeks, though no significant improvement was found on the Wisconsin Card Sorting Test.[213] These results suggest that 5-HT_{2A} receptor antagonism may improve cognitive function in schizophrenia,[214,215] though additional clinical studies are needed. However, because nearly all approved atypical antipsychotic drugs have potent 5-HT_{2A} antagonist actions, it is unlikely that adding on a drug with potent 5-HT_{2A} antagonism will provide any significant boosting of cognition in treated patients.[212] The potential cognition-enhancing effects resulting from 5-HT_{2A} receptor antagonism with the currently available atypical antipsychotics may be masked by other drug actions, such as anticholinergic effects, known to cause cognitive impairment.[216]

5-HT_{1A} Receptors

5-HT_{1A} receptors are densely concentrated in the hippocampus, lateral septum, amygdala, and cortical limbic areas, as well as both the dorsal and median raphe nuclei.[217,218] On raphe neurons, 5-HT_{1A} receptors function as somatic autoreceptors providing inhibitory feedback control of 5-HT release.[219] However, the highest concentrations of 5-HT_{1A} receptors are on cortical and hippocampal pyramidal neurons[220] suggesting a role of 5-HT_{1A} receptors in mediating cognitive functions. 5-HT_{1A} receptors on cortical pyramidal neurons are colocalized with 5-HT_{2A} receptors,[221] though while 5-HT_{2A} receptor activation is excitatory, 5-HT_{1A} receptor activation inhibits pyramidal neurons.[222]

Because they act on different locations of the receptors, both 5-HT_{1A} partial agonists and full antagonists have shown a positive effect on cognitive activity in animals.[223] Thus, 5-HT_{1A} partial agonists, presumably acting on pyramidal neurons, improve cognition in animals, while 5-HT_{1A} antagonists also improve cognition, probably by acting at the raphe autoreceptors.[208,223] Indeed, atypical antipsychotic drugs modestly enhance cognition, and several atypical antipsychotic drugs have 5-HT_{1A} partial agonist actions (eg, aripiprazole, clozapine, olanzapine, ziprasidone, quetiapine),[224,225] while others are 5-HT_{1A} antagonists (eg, risperidone and sertindole).[224] Preclinical experiments also show that both 5-HT_{1A} partial agonists and antagonists can improve cognition. For example, intraprefrontal infusion of 8-OH-DPAT, a nonselective 5-HT_{1A} agonist, improved visual-spatial attention and decreased impulsivity in rats,[226] while WAY100635, a 5-HT_{1A} antagonist, blocked the deleterious effects of MK-801 and NMDA antagonist in rats.[227] Thus, the preclinical literature is mixed regarding whether 5-HT_{1A} agonists or antagonists enhance cognition.

Clinical data in humans are equally mixed. For example, activating 5-HT_{1A} receptors with a single dose of tandospirone, a 5-HT_{1A} partial agonist, diminished explicit memory function[228] in demented patients, though chronic administration of tandospirone enhanced verbal memory in patients with schizophrenia.[229,230] Interestingly, the 5-HT_{1A} agonist NAE-086 actually induced hallucinations and nightmares in normal individuals after repeated doses,[231] suggesting that 5-HT_{1A} agonists may not be tolerated well in schizophrenic individuals. Taken together, these results demonstrate that additional clinical studies are needed but suggest that 5-HT_{1A} receptors may need to be differently modulated to optimally enhance cognition in various pathologic conditions (ie, dementia vs schizophrenia) and that 5-HT_{1A} partial agonists with a high level of efficacy may present a significant risk of exacerbating positive symptoms in schizophrenia.[231]

5-HT_4 Receptors

Serotonin 5-HT_4 receptors are found at high densities in the hippocampus, frontal cortex, and amygdala, suggesting a role of these receptors in cognitive functions.[232,233] Indeed, 5-HT_4 receptors have been shown to be markedly decreased in patients with Alzheimer's disease.[234] In addition, 5-HT_4 receptor agonists have shown promise in the treatment of cognitive impairment by enhancing cholinergic transmission in the hippocampus.[212,235] For example, a 5-HT_4 receptor partial agonist, SL65.0155, improved learning and memory performance in chemically induced rat model of amnesia,[236] and this improvement may be due in part to lengthening of the excitatory postsynaptic potential in hippocampal CA1 pyramidal neurons.[237] Interestingly, a recent study also showed that the activation of 5-HT_4 receptors in a neuronal culture inhibited the secretion of β-amyloid peptide and enhanced neuronal survival.[238] Thus, while 5-HT_4 receptor–selective agonists are mostly being studied for their role in the treatment of Alzheimer's disease, they may also be of benefit in the treatment of the cognitive dysfunction in schizophrenia.

5-HT_6 Receptors

Several atypical antipsychotics, including clozapine and olanzapine, and some tricyclic antidepressants, such as amoxapine, amitriptyline, and clomipramine, were found to have high affinity for 5-HT_6 receptors[239–241] prompting significant efforts to understand its possible role in schizophrenia and other neuropsychiatric disorders. When antisense oligonucleotides were used to decrease the level of 5-HT_6 receptor expression in rats, the rats exhibited an increased number of yawns and stretches that could be blocked by atropine, suggesting a role of the 5-HT_6 receptor in the control of cholinergic neurotransmission.[242,243] In addition, the selective 5-HT_6 receptor antagonist SB-271046 has been shown to improve memory retention in the water maze test of spatial learning and memory.[244,245] Thus, it appears likely that 5-HT_6 receptors may have an important future role in the treatment of cognitive deficits in neuropsychiatric illnesses such as Alzheimer's disease and schizophrenia.[212]

5-HT$_7$ Receptors

The 5-HT$_7$ receptor exhibits a distinct distribution in the central nervous system with relatively high levels in the thalamus, hypothalamus, and hippocampus and lower levels in the cortex and amygdala.[246–248] In addition to possible roles in regulating circadian rhythms and sleep,[249–251] 5-HT$_7$ receptors may also have an important role in hippocampus-dependent functions such as learning and memory.[252] For example, 5-HT$_7$ receptor knockout mice have been found to exhibit a specific impairment in contextual fear conditioning in which the animal learns to associate the environment with an aversive stimulus, a process generally believed to require the hippocampus.[253] Electrophysiological studies have also shown that 5-HT$_7$ receptor activation modulates the excitability and intracellular signaling of pyramidal neurons in the CA1 region of the hippocampus.[254,255] Additionally, in 5-HT$_7$ receptor knockout mice, there is a reduced ability to induce long-term potentiation in the CA1 region of the hippocampus.[253] Together, these findings suggest an important role for the 5-HT$_7$ receptor in hippocampus-dependent functions, including learning and memory.[252] Thus, selective 5-HT$_7$ receptor activators might prove therapeutically useful for the treatment of the cognitive dysfunction of schizophrenia.[212]

Other Neurotransmitter Targets

α_2-Adrenergic Receptors

The central noradrenergic system projects from the locus ceruleus to the prefrontal cortex where α_2-adrenergic receptors appear to play an important role in cognitive functioning.[256] Indeed, treatment with the α_2-adrenergic receptor agonists, clonidine and guanfacine, has been shown to improve cognitive performance without exacerbating positive symptoms in small trials of patients with schizophrenia.[257,258] In addition, patients randomized to risperidone plus guanfacine showed significant improvement on tasks of working memory and attention compared with patients receiving typical antipsychotics plus guanfacine.[258] However, clozapine and other atypicals have potent antagonist properties at α_2-adrenergic receptors,[259] which may contribute to the atypicality of atypicals by preferentially enhancing dopaminergic transmission in the frontal cortex over subcortical dopaminergic pathways.[260] Indeed, combined treatment of a typical antipsychotic with the highly selective α_2-adrenergic receptor antagonist, idazoxan, has been reported to produce a profile of antipsychotic activity similar to clozapine.[261] Thus, as α_2-adrenergic receptor activity may be important in developing new drugs for schizophrenia that can improve cognition, balancing α_2-adrenergic receptor activity to achieve both antipsychotic and procognitive efficacy may be challenging.

GABA$_A$ Receptors

Appropriately synchronized GABA neurotransmission in the dorsolateral prefrontal cortex is required for adequate working memory,[262] suggesting that impairments in GABA-mediated inhibition could contribute to the cognitive impairments in schizophrenia. Indeed, postmortem studies have shown reduced GABAergic transmission in schizophrenia.[263–265] In addition, recent observations[266,267] have noted decreases in messenger RNA levels for glutamic acid decarboxylase 67, the synthetic enzyme for GABA, selectively in the prefrontal cortex of patients with schizophrenia. Interestingly, a recent study revealed that GABA alterations in the dorsolateral prefrontal cortex of schizophrenic patients may be restricted to certain cell classes, such as the chandelier cells, which synchronize the activation of pyramidal neurons via GABA$_A$ receptor subtypes.[268] Thus, the use of new benzodiazepine-like agents—selective for the α_2 subunit of the GABA$_A$ receptor—in cognitive disorders could be both interesting and revealing. Indeed, there is evidence that reduced GABA neurotransmission in chandelier cells may be secondary to altered NMDA receptor function and could represent a ''final common pathway'' of prefrontal dysfunction in schizophrenia.[269] 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 GABA$_A$ receptors containing α_2 subunits (eg, a GABA$_A$ α_2-selective benzodiazepine) may improve working memory function in schizophrenia.[270] However, drugs that directly activate α_2-containing GABA$_A$ receptors independent of the presence of GABA may disrupt the critical synchronization of this circuit and impair working memory.[269] In addition, activation of GABA$_A$ receptors containing other subunits (eg, α_1 or α_5), such as by currently available benzodiazepines, may impair cognitive function. Indeed, a recent study in healthy volunteers showed that, contrary to lorazepam, a GABA$_A$ α_2/α_3 subtype–selective partial agonist, TPA023, caused no detectable memory impairment.[271]

As activation of GABA$_A$ receptors containing α_5 subunits, such as by currently available benzodiazepines, may impair cognitive function and cause sedation, inhibitors of these receptors have been hypothesized to enhance cognition. Indeed, functionally selective inverse agonists at α_5-containing GABA$_A$ receptors have been demonstrated to enhance performance in animal models of cognition,[272–274] apparently without lowering the seizure threshold as seen with nonselective GABA$_A$ inverse agonists.[274,275] In addition, α_5 subunit knockout mice demonstrate increased hippocampal activity due to the release of tonic GABAergic inhibition.[276] Thus, antagonists or inverse agonists at α_5-containing GABA$_A$ receptors may hold promise in the treatment of the cognitive dysfunction in schizophrenia.

Neurosteroids and Sigma Receptors

The sigma (σ) receptor was initially designated as a subtype of opioid receptors[277] but was later found to be a distinct pharmacological entity due to lack of binding of the classical opiate receptor antagonists naloxone and naltrexone.[278] Indeed, when the σ1 receptor was isolated and cloned, it was found to have no structural similarity to the opioid receptors.[279] The functions of these receptors are poorly understood and endogenous ligands have yet to be identified, though it has been proposed that steroid hormones (eg, progesterone and testosterone), drugs of abuse (eg, cocaine, heroin, PCP), and psychiatric drugs (haloperidol, imipramine, and sertraline) may interact with σ receptors.[280,281] In addition, it is well documented that σ1 receptor ligands increase the NMDA receptor response in the hippocampus,[282–284] suggesting a role in enhancing cognition. Indeed, σ1 receptor agonists can reverse the memory impairments induced by the NMDA antagonists MK-801 in rodents.[285]

Neurosteroids, such as dehydroepiandrosterone (DHEA) and allopregnanolone, have been implicated in neuroprotection[286–288] and enhancement of NMDA receptor neurotransmission,[287,289,290] possibly through interaction with σ1 receptors,[290] suggesting therapeutic potential for enhancing cognition in schizophrenia. Consistent with the enhancement of NMDA neurotransmission, DHEA can enhance memory in rodents.[291–294] In humans, a double-blind study of DHEA as an adjunct to antipsychotic treatment in chronic schizophrenic patients with prominent negative symptoms suggests some efficacy at improving negative symptoms, especially in women,[295] though further studies are needed. Thus, neurosteroids may have therapeutic potential for improving the cognitive deficits observed in schizophrenia, though long-term treatment with steroids is problematic. In addition, while the contribution of σ receptor agonism to the actions of neurosteroids is not entirely known, highly selective σ receptor agonists are needed and hold therapeutic promise.

Potential Future Targets

There are a number of additional largely theoretical pharmacotherapeutic approaches for the treatment of cognition and schizophrenia. For example, significant progress has been made in recent years on elucidating various susceptibility genes in schizophrenia, including dysbindin, neuregulin 1, COMT, DISC1, and others.[296] Interestingly, many of these genes appear to be related to the control of synaptic plasticity and glutamate transmission (particularly NMDA receptor function) and thus may allow for hypothesis-driven approaches for developing of actual disease-modifying drugs for schizophrenia and cognitive disorders.[297] Another strategy involves the role of neurotrophic factors in the pathophysiology of schizophrenia and the theory that schizophrenia may involve a neurodegenerative process.[298] Neurotrophic factors, such as brain-derived neurotrophic factor, may play a role in neuronal and glial differentiation, proliferation, and regeneration and influence synaptic organization, neurotransmitter synthesis, and the maintenance of synaptic plasticity.[299,300] Thus, strategies to enhance neurotrophic factor action may be able to prevent progression of schizophrenia.

Altering neurotransmitter signaling by targeting intracellular signaling cascades has long been suggested to be a future approach to novel therapeutic agents.[301] Though there has been concern about the feasibility of this approach, lithium is a signal transduction modifier that has been used safely for decades. Some targets being investigated include protein kinase C isoforms and glycogen synthase kinase 3.[302] In addition, subtype-selective phosphodiesterase (PDE) inhibitors, particularly at PDE10A, are actively being explored for the treatment of various symptom domains in schizophrenia.[303] Another interesting approach at the receptor level would be developing ligands that differentially activate the various signaling pathways mediated by a single receptor, a process termed "functional selectivity".[304] Indeed, functional selectivity has been described in serotonin, opioid, dopamine, vasopressin, and adrenergic receptor systems[304] and may be initiated by different ligand-induced conformational states, as shown for the β_2-adrenergic receptor.[305] Thus, the possibility of selecting or designing novel ligands that differentially activate only a subset of receptor functions is intriguing as an approach to drug discovery that may optimize therapeutic action.

Conclusions

Cognitive dysfunction is a major feature of schizophrenia that contributes significantly to the long-term functional impairment that patients experience. While the past half-century of antipsychotic development has had a profound effect on the treatment of schizophrenia, the cognitive deficits in schizophrenia have been insufficiently addressed. Therefore, it is critical to continue the pursuit of diverse molecular targets for discovering new pharmacotherapeutic agents for the treatment of schizophrenia. For the past 20 years, psychopharmacologic research in schizophrenia has aimed for the development of new antipsychotic drugs with a more rapid onset of action, lower risk of side effects, and improved efficacy in the domains of negative and cognitive symptoms from a single compound. Currently, however, it seems unlikely that a single drug will have the desired effect across all these domains, and thus, optimal treatment of schizophrenia will likely rely on individualized polypharmacy and augmentation strategies. The ultimate goal, of course, will be the development of "cure therapeutics"[297] which will require significant advances in our understanding of the

underlying pathophysiology of schizophrenia, highlighting the need for continued basic research efforts at identifying and validating diverse and novel molecular targets.

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