Review

Alpha7 Nicotinic Receptors as Therapeutic Targets in Schizophrenia

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Abstract

While current treatments for schizophrenia often provide much relief for positive symptoms such as hallucinations, other symptoms, particularly cognitive deficits, persist and contribute to substantial suffering and reduced quality of life for patients. In searching for novel therapeutic avenues to treat cognitive deficits in schizophrenia, recent work is exploring nicotinic receptor neurobiology. Supported by a large body of evidence, with contributions from studies of smoking behaviors, genetics, receptor distribution and function, animal models and nicotinic effects on illness symptoms, the alpha7 nicotinic receptor has emerged as a potential therapeutic target. Despite promise in early clinical trials, however, no drug targeting nicotinic systems has succeeded in larger phase 3 trials. Following a brief review of nicotinic receptor biology and the evidence that has led to pursuit of alpha7 nicotinic agonism as a therapeutic strategy, this review will provide an update on the status of recent trials, discuss potential issues that may have contributed to negative outcomes, and point to new directions and promising advances in developing alpha7 nicotinic receptor-based treatment for cognitive symptoms in schizophrenia.

Implications: By examining alpha7 nicotinic receptor biology and recent efforts to target the receptor in clinical trials, it is hoped that investigators will be motivated to explore novel, promising directions focusing on the receptor as a strategy to treat cognitive symptoms in schizophrenia.

Introduction

The earliest known human use of nicotine likely dates back 7000 years.¹ Following its discovery by the Europeans in the 1400s, the drug's use expanded greatly, such that nicotine is now arguably the most widely used drug of abuse, as it has been for the last 400 years.² Its most commonly used form, the tobacco cigarette, combines nicotine with potent carcinogens to create a substantial and ongoing public health concern. Cigarette smoking is linked to cancer and other diseases in nearly every organ within the body. From 2000 to 2004 alone, smoking is estimated to have caused 393 000 premature deaths annually.³ Vaporized nicotine from cigarette smoke contributes to this morbidity and mortality by inducing rapid dopamine release in brain reward regions, such as the ventral

striatum, facilitating a potent addictive behavior. Like many poisons in the history of medicine, however, some of the same properties that make nicotine harmful may provide the basis for useful novel therapeutics. Specifically, nicotine's ability to cross the blood–brain barrier and alter signaling at specific receptors may provide a basis for novel drugs aimed at addressing unmet therapeutic needs in schizophrenia, Alzheimer's disease, and other psychiatric disorders. Through targeting nicotine-sensitive receptors, it is hoped that these potential drugs can harness the beneficial properties of nicotinic signaling within the brain, while avoiding the addictive and harmful effects of nicotine itself.⁴

As an example, cognitive dysfunction in schizophrenia is an unmet therapeutic need, and is a focus of ongoing clinical trials. Cognitive symptoms, encompassing problems with working memory,

selective attention, and executive function, are distinct from the cardinal “positive” symptoms of the illness, such as hallucinations and delusions. Importantly, cognitive symptoms are related to indicators of poor quality-of-life such as chronic unemployment, social difficulties, depression, and suicide risk.^{5,6} Current pharmacologic treatment for schizophrenia often is largely effective at reducing positive symptoms by targeting dopaminergic receptors. By helping to ameliorate these symptoms, antipsychotic medications often allow acutely ill inpatients in psychiatric hospital wards to transition to outpatient treatment. These medications are, however ineffective in treating cognitive symptoms. Consequently, they do not address much of the suffering associated with schizophrenia or the difficulties faced by individuals with the disease.

This unmet therapeutic need may cause individuals with schizophrenia to seek out additional solutions to ease their suffering. One possible avenue for this may be nicotine. Smoking rates in schizophrenia are high, ranging as high as 70%, higher than in any other psychiatric disease.⁷ While many possible mechanisms may contribute to this high smoking rate, studies examining the biology of schizophrenia, as well the effects of nicotine on cognition, suggest that increased nicotine use in the disease may be a form of self-medication aimed at improving cognition.^{8,9} As will be briefly discussed in this review, investigations have provided direct support for this hypothesis, leading to ongoing clinical trials attempting to target cognitive dysfunction in schizophrenia with nicotinic agonists.

Despite promising results in many early trials, however, no pharmaceutical compound targeting nicotinic receptors has received FDA approval to treat cognitive dysfunction in schizophrenia. Unforeseen obstacles have arisen, likely due to the complicated biochemistry of nicotinic receptors and their responses to ligand binding. In the following sections, we review the pharmacology of nicotine and the evidence for nicotinic dysfunction in schizophrenia, before offering an overview of current and ongoing clinical trials. Lastly, we will discuss recent promising developments in preventative treatment for cognitive dysfunction in schizophrenia, aimed at decreasing the disease burden long before the onset of symptoms.

The Pharmacology of Nicotinic Receptors

Nicotine is the exogenous ligand of the nicotinic family of acetylcholine receptors (nAChR), members of a broader class of ligand-gated ion channels that includes GABA-A and serotonergic 5-HT₃ receptors.^{10,11} In mammals, neuronal nAChRs are coded by 11 genes expressing receptor subunits (alpha2-alpha7, alpha9, alpha10, beta2-beta4). Subunits assemble into five-membered rings surrounding a central cation channel, forming functional nAChRs. In response to binding acetylcholine or nicotine, the cation channel opens to allow influx of Na⁺ or Ca²⁺ into the cell. Two types of receptor assemblies exist, differing in their constituent subunits and pharmacology. Heteromeric nAChRs consist of three alpha subunits combined with two beta subunits, commonly alpha4beta2 in the brain. Homomeric nAChRs, originally identified due to selective binding of the snake venom alpha-bungarotoxin, assemble from a single subunit type, typically alpha7 in the human brain.^{2,10} Homomeric alpha7 nAChRs are highly permeable to Ca²⁺, exceeding the permeability of NMDA receptors.¹² Anatomically, alpha4beta2 nAChRs are widely expressed in the cortex and subcortical areas in humans, while alpha7 nAChRs are more selectively expressed, with the highest concentrations being in the hippocampus, the thalamic reticular nucleus, as well as the lateral and medial geniculate nuclei.^{13,14} On

the cellular level, both receptor types are expressed both pre- and postsynaptically. Presynaptic nAChRs, positioned to allow Ca²⁺ influx into the synaptic bouton, play a major role in modulating the release of many neurotransmitters.^{10,11}

Physiologically, the two types of nAChRs differ in their affinity for nicotine and rate of desensitization in response to ligand binding. Alpha4beta2 nAChRs bind nicotine with high affinity, and produce a sustained response. Subsequently, they desensitize, transitioning to a temporarily unresponsive state, relatively slowly in comparison with other nAChRs. In contrast, alpha7 nAChRs are less responsive to nicotine, produce a rapid response, and desensitize quickly following ligand binding.^{15,16} The receptor types differ in their long-term responses to nicotine exposure as well. Interestingly, in a phenomenon known as paradoxical up-regulation, alpha4beta2 receptor expression increases in response to smoking.¹⁷ In contrast, up-regulation of alpha7 nAChRs in the brains of smokers is minimal.^{10,18}

Cigarette smoking produces daily cycles of nAChR stimulation, saturation, and desensitization, followed by partial re-sensitization. Nicotine vapor is rapidly absorbed by pulmonary circulation, transported to the brain, and thereafter rapidly metabolized in the liver, with a half-life of 2 hours.¹⁹ With infrequent smoking, nicotine levels rise and fall relatively quickly, nAChR desensitization is initially minimized, and a brief period of abstinence, such as overnight sleep, restores nAChR function. In contrast, repeated cigarette use during the day creates near-complete saturation and desensitization of alpha4beta2 receptors in the brain.²⁰ Chronic smoking produces sustained elevation of nicotine levels in the body, detectable during the day and night.¹⁹

Nicotinic Dysfunction in Schizophrenia

Smoking rates in schizophrenia range as high as 70%, which is higher than in any other psychiatric disease.⁷ Smokers with schizophrenia also extract more nicotine per cigarette, likely via smoking behaviors such as occluding cigarette filter pores and/or prolonged inhalation, and smoke more cigarettes per day than smokers in the general population.^{21,22} The reasons for this heavy nicotine use are unknown, but may be an attempt to activate low-affinity alpha7 nAChRs.

Genetic studies link nicotinic dysfunction, particularly that involving the alpha7 nAChR, to schizophrenia as well. Single nucleotide polymorphisms (SNPs) in the upstream regulatory region of the gene that codes for the alpha7 nAChR, CHRNA7, are associated with increased risk of developing the illness.²³⁻²⁹ Deletions of CHRNA7 are associated with schizophrenia and related psychoses.³⁰ Additionally, CHRNA7 mRNA is decreased in the dorsolateral prefrontal cortex and hippocampus of patients with schizophrenia.^{31,32} In the reticular nucleus of the thalamus, alpha7 nAChR expression is decreased in subjects with schizophrenia, as measured by alpha-bungarotoxin binding.³³

Functionally, nicotine or nicotinic agonists normalize many of the sensory processing deficits found in schizophrenia. These include electrophysiological measures of sensory processing such as P50 sensory gating, pre-pulse inhibition, and smooth pursuit eye movements. The P50 sensory gating paradigm uses electroencephalography (EEG) to assess the inhibition of neuronal evoked responses to repeated pulses of auditory stimuli. Typically recorded from the vertex (top of the scalp), the paradigm examines a positively directed wave with a 50 millisecond latency that, in healthy subjects, shows a consistent response to initial stimuli, but then is inhibited, or gated, in response to subsequent, repeated stimuli. Patients with schizophrenia fail to gate P50 responses to repeated stimuli, however, suggesting a deficit

in early inhibitory mechanisms in the illness, one that is temporarily normalized by smoking.³⁴ Similarly, pre-pulse inhibition (PPI) measures the inhibitory effect of a weak stimulus occurring prior to a startling stimulus. Although it can be observed across multiple modalities, this response in humans is most often studied using auditory stimuli, examining the eye-blink component of the startle response, measured by electromyography (EMG). Healthy subjects show decreased startle response to the louder stimulus when preceded by a weaker stimulus, suggesting an inhibitory mechanism. In patients with schizophrenia, the startle response is not inhibited by the first stimulus, an abnormality that is also improved by smoking.³⁵ The smooth pursuit eye movement task measures the accuracy of eye movements following a moving target. Performance of the task, often studied with infrared measurement techniques, is abnormal in schizophrenia, with the deficit also being transiently improved by nicotine.³⁶ This improvement in eye-tracking in response to nicotine has been shown to be related to neuronal activity in the hippocampus and anterior cingulate gyrus, both regions which are rich in cholinergic innervation.^{37,38}

In addition to improving sensory processing deficits, some of the cognitive deficits commonly found in schizophrenia are improved by nicotine. In animal models, nicotine improves performance on learning and memory tasks.^{39,40} In patients with schizophrenia, nicotine improves performance on attention and working memory tasks, though the duration of the effects is unknown.^{41–44} The effects of nicotine on attention can be blocked by the nonselective nAChR antagonist mecamylamine.⁴³

The above evidence suggests that schizophrenia is linked to dysfunction of nicotinic systems, and that the cognitive deficits in the disease are improved with nicotine administration. However, developing nicotine itself into a therapy is challenging and problematic. Nicotine has a low therapeutic index with adverse effects such as anxiety, nausea/vomiting, and mood changes.⁴⁵ In addition, the pharmacology of nicotinic receptors limits nicotine's potential as a therapy. Long-term nicotine use may result in tachyphylaxis, a decrease in drug effects after repeated exposures, for at least some cognitive tasks.⁴⁴ This effect is likely related to the acute sensitivity of all nAChRs, as they desensitize in response to ligands. As such, in the context of examining nicotine as a therapeutic agent for schizophrenia, the smoking status of potential subjects affects their response to nicotine on cognitive tasks. After brief abstinence from nicotine for 2–3 hours, smokers with schizophrenia potentially show both increased⁴² or decreased⁴⁴ response to nicotine on cognitive tasks, compared to nonsmokers with the disease.

As a consequence of these challenges presented by nicotine itself, the search for nicotinic therapies for cognitive dysfunction has focused on other small molecules. These potential drugs target the same receptors as nicotine, often with greater specificity for particular nAChRs, while attempting to avoid nicotine's detrimental effects. Due to promising preclinical trials in animal models, most potential drug compounds currently under development specifically target the alpha7 nAChR. While some compounds targeting nAChRs failed in phase 1 clinical testing due to cardiac side effects, many others succeeded with mild side effect profiles and promising cognitive effects. In recent years, these potential nicotinic therapies have progressed to ongoing phase 2 and phase 3 trials.

Clinical Trials of Nicotinic Therapies in Schizophrenia

The first potential nicotinic therapy targeted for drug development in schizophrenia was 3-(2,4-dimethoxybenzylidene)-anabaseine

(DMXB-A). Derived from the toxin of marine nemertine worms, DMXB-A is primarily a partial agonist at alpha7 nAChRs, though it also shows activity at alpha4beta2 receptors.⁴⁶ Early clinical safety trials in healthy subjects demonstrated a short half-life of approximately 1 hour, promising effects on cognition, and minimal side effects.⁴⁷ DMXB-A subsequently was evaluated in phase 2 trials in clinical populations. Single-dose administration in nonsmokers with schizophrenia demonstrated significant improvements in both P50 sensory gating and cognition, compared to placebo.^{48,49} In this trial, a lower dose of the drug appeared to be more effective in improving cognitive dysfunction in the disease. Subsequently, DMXB-A effects were examined in a larger trial, in which nonsmokers with schizophrenia were treated with two different DMXB-A doses and placebo for 4 weeks, in a crossover design. DMXB-A treatment was associated with an improvement in negative symptoms, and a nearly significant improvement in positive symptoms. While no treatment effects were observed on the primary cognitive outcome measure, an effect interpreted as related to unanticipated practice effects, secondary analyses examining only the first treatment arm, which eliminated practice effects, found that DMXB-A treatment was associated with improved attention and working memory.^{48,49} DMXB-A was also found to reduce neuronal hyperactivity of the hippocampus and of the posterior default network in patients.^{50,51} Subsequently, due to the short half-life of DMXB-A (Table 1), the next trial used a slow-release formulation taken four times daily. Additionally, in order to better match the general schizophrenia population, smoking subjects were included. Compared to the previous immediate-release formulation, extended exposure to slow-release DMXB-A resulted in a greatly diminished response, with no observable effects attributable to DMXB-A at any tested dose, in smokers or nonsmokers.⁶⁰ The results were confounded by very low drug plasma levels in smokers, and interpreted as evidence that extended desensitization of nAChRs, caused by the slow-release drug, may complicate efforts to develop nicotinic therapies.

Encenicline, or EVP-6124, is alpha7 partial agonist that was recently evaluated in late phase clinical testing for treating cognitive dysfunction in schizophrenia. In addition to binding at alpha7 nAChRs, it is also a serotonergic 5-HT3 antagonist. In contrast to DMXB-A, encenicline has a long half-life of 50 or more hours (Table 1). Preclinical results in animal models of cognitive dysfunction, as well as early clinical trials of the drug in healthy subjects, were promising and showed a mild side effect profile and beneficial effects on cognition.⁵² Subsequent studies in patients with schizophrenia tested a once-daily administration at two dosing levels over a period of 12 months, in both smokers and nonsmokers with the

Table 1. Half-Lives of Compounds Targeting Alpha7 Nicotinic Receptors

Compound	Alpha7 activity	Half-life
DMXB-A	Partial agonist	1 h ⁴⁷
Encenicline (EVP-6164)	Partial agonist	50–65 h ⁵²
AQ051	Partial agonist	19–46 h ⁵³
ABT-126	Partial agonist	34 h ⁵⁴
RG3487	Partial agonist	Not reported
Tropisetron	Partial agonist	6–8 h ⁵⁵
TC-5619	Full agonist	20 h ⁵⁶
AVL-3288	PAM	3 h ⁵⁷
Galantamine	PAM	7 h ⁵⁸
JNJ-39393406	PAM	6 h ⁵⁹

disease. Consistent beneficial effects from the drug were observed across multiple measures of cognition, with greater effects observed at the smaller dose for the primary endpoint.⁶¹ No observable effects of smoking status were noted, but subjects were required to abstain from nicotine for a short period before testing. Following these positive results, encenicline advanced to phase 3 clinical trials for cognitive dysfunction in schizophrenia and Alzheimer's disease. In contrast to earlier trials, these later trials have raised problematic concerns about side effects and efficacy. The phase 3 clinical trial of encenicline in Alzheimer's disease was halted due to gastrointestinal side effects.⁶² In schizophrenia phase 3 trials, encenicline failed to meet primary endpoints relating to improvements in cognition.^{62,63}

Similar results have been observed for other alpha7 nAChR partial agonists. AQW051, another drug developed to target alpha7 nicotinic receptors, has shown promising results in early clinical trials.⁵³ In patients with schizophrenia, AQW051 modifies neuronal activity in prefrontal and hippocampal regions. However, it does not appear to improve cognition and may worsen working memory performance in smokers at high doses.⁶⁴ Similarly, the alpha7 partial agonist ABT-126 improved cognition in nonsmokers, but not smokers, with schizophrenia in a phase 2 trial.^{65,66} While the side effect profile of ABT-126 is minimal, it does include constipation.⁶⁵ Similar to these results, phase 2 trials of the alpha7 partial agonist RG3487 had a nonsignificant effect on cognition in schizophrenia and included constipation as a side effect.⁶⁷ Lastly, the serotonergic 5-HT3 antagonist tropisetron, currently used to treat chemotherapy-induced nausea and vomiting, is a partial alpha7 nAChR agonist as well. In schizophrenia, tropisetron improves electrophysiological measures of sensory gating such as P50, as well as cognitive measures in nonsmoking subjects.⁶⁸ Similar to other alpha7 agonists, constipation and abdominal pain were significant side effects.

Clinical trials of a full alpha7 nAChR agonist have yielded similar results to the partial agonists highlighted above. TC-5619 initially showed great promise for treating cognitive symptoms in preclinical animal models.⁶⁹ Early clinical testing in patients with schizophrenia demonstrated modest, if inconsistently present, improvements in cognitive measures, with mild gastrointestinal side effects.⁵⁶ Larger phase 2 trials of TC-5619 at higher doses did not show a significant effect, suggesting that the initial success may be due to the lower drug dose administered in previous trials.⁷⁰

Positive allosteric modulators (PAMs) are an alternative strategy for increasing alpha7-related neurotransmission. As opposed to agonists discussed above, which activate receptors directly by binding at the primary (orthosteric) ligand site, allosteric modulators instead affect receptor function by interacting at secondary, or allosteric, binding sites, where they facilitate the effects of endogenous neurotransmitters. Importantly for nAChRs, PAMs are less likely to cause desensitization. As a prototypical example of a successful PAM, the anti-anxiety medication diazepam is a model PAM that facilitates GABA binding, leading to reduced symptoms with minimal side effects. Several PAMs targeting alpha7 nAChRs have shown promise for treating cognitive dysfunction in preclinical trials using animal models, and are now in early phase clinical testing in humans. AVL-3288, currently in safety testing in healthy subjects, improved P50 sensory gating in a phase I clinical trial, with positive but nonsignificant improvement in cognition and minimal side effects.⁵⁷ Type 1b clinical trials of AVL-3288 in schizophrenia are underway.⁷¹ Galantamine, an alpha7 PAM and acetylcholinesterase inhibitor, in combination with choline, an endogenous alpha7 nAChR ligand, showed positive moderate effect sizes for cognitive and symptom

measures, but again, effects on these primary outcome measures were not statistically significant. Treatment effects were significant, however, for secondary outcome measures of global functioning and memory. Side effects included gastrointestinal symptoms.⁷² Trials of alpha7 PAMs that counteract receptor desensitization have been less successful. The alpha7 PAM JNJ-39393406 did not show any appreciable effect on P50 sensory gating or cognitive measures in smokers with schizophrenia.⁷³

In summary, many studies have now investigated the potential therapeutic effects of therapies targeting alpha7 nAChRs for treating cognitive dysfunction in schizophrenia (Table 1). Many compounds showed promising results in preclinical trials, as well as in early phase 1 and 2 clinical trials. To date, while final results for some investigations are pending, the earlier promising results for most alpha7-targeting drugs currently in development have not translated into successful phase 3 clinical trials. As discussed in the following section, future investigations will need to build upon both the successes from these previous trials, as well as learn from the unexpected complications previously encountered.

Looking Forward: Continued Development of Nicotinic Therapies

Drug development is, above all, an ongoing process in which the information learned at one stage is used to facilitate advancement at the next. To date, no compound developed to target alpha7 nAChRs is a clear and unqualified success story, in terms of meeting the primary endpoint of a successful phase 3 clinical trial. However, the earlier successes in many phase 1 and 2 trials can be built upon, providing the information needed to guide future clinical trials targeting the alpha7 nAChR.

Many of the themes that emerged in the above overview of current clinical trials may be related to the effects of receptor desensitization. All neuronal nAChRs become temporarily inactive after prolonged exposure to an agonist.⁷⁴ Alpha7 nAChRs, in particular, rapidly become desensitized in response to ligand binding. As a result, low concentrations of a nAChR agonist may be more effective than higher concentrations, as the latter will maintain receptors in a desensitized and unresponsive state. In animal models, the greatest response to a nAChR agonist is often observed with a low drug dose. Increasing dose levels often produces a decreasing effect, in an inverted U-shaped response curve, which may be due to receptor desensitization, as well as other nonlinear effects on physiologic systems. As an example, in primates, a low dose of an alpha7 nAChR agonist facilitates prefrontal neuronal functions and related cognitive tasks, an effect that is not observed at higher doses.⁷⁵

Many of the alpha7 clinical trials have found greater efficacy at lower doses. This is true for DMXB-A,⁴⁸ encenicline,⁶¹ and was hypothesized to explain successful early trials of TC-5619.⁷⁰ If confirmed, these results suggest that the inverted U-shaped response curve for alpha7 agonists peaks at a very low dose. Beyond this peak, higher doses will likely result in minimal or no improvement on cognition, as increasing drug concentrations primarily and counterproductively contribute to receptor desensitization.

The contrasting results of immediate and slow-release DMXB-A trials are particularly informative about the potential consequences of nAChR desensitization. Once absorbed into the circulatory system, DMXB-A has a short half-life of 1 hour. The immediate release formulation is quickly absorbed, and showed significant effects on cognition and P50 sensory gating in schizophrenia.^{48,49} In contrast,

the slow release formulation encapsulates DMXB-A in a digestible hypromellose polymer, slowing absorption of the drug to 4 hours. Despite reaching comparable plasma levels as the immediate release formulation, the slow release DMXB-A formulation did not affect cognition or sensory gating in schizophrenia.⁶⁰ In this case, the immediate release formulation allowed rapid absorption of the drug followed by clearance, and likely minimized desensitization, resulting in a significant response. In contrast, slow absorption of the same concentration of drug did not show an effect, possibly due to maintaining the receptors in a desensitized state.

A similar desensitization process likely occurs with chronic nicotine exposure in smokers,⁴⁴ potentially explaining some of the observed differential effects between smoking and nonsmoking subjects. Most investigations of alpha7 agonists that showed a positive effect on cognition in schizophrenia consisted entirely of nonsmoking subjects,^{48,49,68} or the results were limited to a nonsmoking subgroup.⁶⁶ In contrast, investigations including both smoking and nonsmoking subjects with schizophrenia, or only including smoking subjects, did not show an effect on cognition.^{60,67,70} In one case, high doses of an alpha7 partial agonist worsened performance on a working memory task in smoking subjects, but not in nonsmokers.⁶⁴ Chronic tobacco use may saturate and complete desensitization of alpha7 nAChRs, preventing the drugs from reaching their molecular target, similar to the complete saturation observed for alpha4beta2 nAChRs after smoking.²⁰

In addition to the challenges presented by nAChR desensitization, other reasons may contribute to the discrepancy between promising preclinical and early phase clinical trials and disappointments in later phases. In preclinical trials, the larger effect sizes in animal models of cognition and response to alpha7 nAChR agonists may be due to species-specific differences in receptor sensitivity.⁷⁶ Additionally, statistical issues, such as insufficient multiple comparison control and an emphasis on results of secondary analyses, may lead to false positives in many early phase clinical trials, including the trials of alpha7 agonists discussed in this review.⁷⁷ Recent investigations have also suggested that factors such as unanticipated practice effects may influence the cognitive symptom measures used in these trials, possibly masking a positive outcome.⁴⁹ Lastly, systemic issues in the conduct of phase 3 clinical trials, such as inexperienced trial sites, counterproductive financial incentives, and inadequate dosing information from earlier trials, may also contribute.⁷⁸

Looking to the future of nicotinic therapies for cognitive dysfunction, there is reason for cautious optimism. Clinical trials of alpha7 PAMs are in early phases and will likely avoid problems with receptor desensitization. The systemic issues in clinical trials can be addressed with careful attention to study methodology and analysis.⁷⁸ Finding the optimal dose of an alpha7 agonist that will minimize desensitization is a challenge, but not an insurmountable one. The use of more objective, intermediary biologic markers related to cognition, such as P50 sensory gating, can be helpful in this regard, as can the use of translational functional magnetic resonance imaging (fMRI) to refine animal models of cognition and determine optimally effective drug doses.^{78,79} The success of this strategy will depend, however, on rigorous validation of these potential biomarkers. Lastly, as will be discussed below, in addition to clinical trials of nAChR agonists and PAMs, recent results have raised the hope that a nicotinic therapy may be able to impact adult cognitive dysfunction if administered early in development, even potentially in utero.

Preventative Medicine for Cognitive Dysfunction

Acetylcholine is not the only endogenous ligand for alpha7 nAChRs. Choline, its chemical precursor, is an alpha7 ligand and plays an important role during development of the cholinergic system. Alpha7 nAChRs respond to the micromolar concentrations of choline found in amniotic fluid.^{80,81} Alpha7 nAChRs, along with associated mRNA from *CHRNA7*, are present in the cortex and hippocampus early in development and peak in the period leading up to birth.^{82,83} However, cholinergic innervation from basal forebrain nuclei does not reach these areas until birth or shortly thereafter.^{84,85} Similarly, nAChRs are expressed in these regions before the appearance of choline acetyltransferase, the enzyme necessary to synthesize their primary ligand, acetylcholine.^{86,87} In the absence of acetylcholine, alpha7 nAChRs are likely activated by choline.^{81,87}

Unlike exposure during pregnancy to exogenous nAChR agonists such as nicotine, which causes numerous negative effects, including preterm delivery, fetal growth restriction, sudden infant death syndrome, and congenital anomalies,³ nAChR activation via the endogenous agonist choline is critical during fetal development. In addition to its role as an alpha7 ligand, it acts a methyl donor in many biochemical reactions, influences stem cell proliferation and apoptosis, and stabilizes cell membranes as part of phospholipids, among other roles.⁸⁸ During pregnancy, the needs of the growing fetus can overwhelm the mother's ability to supply choline from dietary intake and synthesis, resulting in detrimental effects on neuronal development. Maternal choline intake and plasma levels are associated with cognition in newborn infants and young children.^{89,90} In animal models of schizophrenia, perinatal choline supplementation improves sensory gating deficits and increases alpha7 nAChRs in the hippocampus.⁹¹ These results suggest that it may be possible to decrease or prevent cognitive dysfunction in schizophrenia through interventions that increase choline early in development.

In a recent clinical trial, dietary supplementation of choline during pregnancy improved P50 sensory gating in newborns with a *CHRNA7* genotype associated with schizophrenia.⁹² Furthermore, in the follow-up longitudinal investigation, maternal choline supplementation improved behavioral measures of attention and social withdrawal in offspring.⁹³ These cognitive symptoms are present in schizophrenia, autism spectrum disorders, and attention deficit hyperactivity disorder. Cognitive benefits of choline supplementation may, therefore, potentially extend beyond schizophrenia to impact many other psychiatric diseases. In these studies, dietary supplementation with a simple prenatal vitamin, choline, improved behavior as well as sensory gating and neuronal inhibition. Informed in part by these studies, the American Medical Association recently recommended increasing choline in all prenatal vitamins.⁹⁴ The implementation of this recommendation will require the cooperation of public health advocates, prenatal vitamin manufacturers, obstetricians, and family physicians. Although the full impact will not be felt for decades, the search for nicotinic therapies for cognitive dysfunction in schizophrenia has resulted in at least one promising success story.

Funding

This work was supported by NIH grants (R01MH102224 and R01DK103691), a Veterans Administration grant (I01CX000459), and the Brain & Behavior Research Foundation.

Declaration of Interests

None declared.

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