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Nicotinic Mechanisms in the Treatment of Psychotic Disorders: A Focus on the α7 Nicotinic Receptor

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Abstract

Nicotine is heavily abused by persons with schizophrenia. Nicotine better enables people with schizophrenia to filter out extraneous auditory stimuli. Nicotine also improves prepulse inhibition when compared to placebo. Nicotine similarly increases the amplitude of patients' duration mismatch negativity. The 15q13-14 region of the genome coding for the α7 nicotinic receptor is linked to schizophrenia. Multiple single nucleotide polymorphisms have been identified in this 15q13-14 gene promoter region that are more frequently present in people with schizophrenia than in normal controls. Abnormalities in expression and regulation of central nicotinic cholinoceptors with decreased α7 binding in multiple brain regions are also present. Nicotine enhances cognition in schizophrenia. Alternative agents that activate the nicotinic receptor have been tested including 3-[2,4-dimethoxybenzylidene]anabaseine (DMXB-A). This compound improved attention, working memory, and negative symptoms in an add-on study in non-smoking patients with schizophrenia. There are multiple other nicotinic agents, including positive allosteric modulators, in the preclinical stages of development. Finally, the effects of varenicline and clozapine and their relation to smoking cessation are discussed.

Keywords

Nicotine; Prepulse Inhibition; P50-evoked potential; α7 nicotinic receptors; Cognition; CHRNA7; CHRNA3; Smoking

1 Smoking in Schizophrenia

Nicotine is heavily abused by persons with schizophrenia. About 90% of patients smoke compared to only 33% in the general population and 45–70% in patients with other psychiatric diagnoses (Hughes et al. 1986; Diwan et al. 1998; Lasser et al. 2000; De Leon et al. 1995). Schizophrenia patients also extract 1.3 times more nicotine from each cigarette than other smokers as evidenced by increased nicotine and cotinine levels, despite smoking a similar number of cigarettes per day, presumably by deeper inhalation (Olincy et al. 1997; Williams et al. 2005). After 12 h of abstinence, in samples matched on gender, smoking levels, and level of nicotine dependence, people with schizophrenia had significantly higher increases in blood nicotine in the first 4 min after smoking than controls; however, total time smoking over 120 min was no different (Williams et al. 2010) The high level of smoking in schizophrenia patients has been proposed as a form of self-medication to alleviate symptoms of their illness including depression, anxiety, anhedonia, or amotivation (Glassman 1993;

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Svensson et al. 1990; Tung et al. 1990; Nisell et al. 1995). Others have proposed that smoking alleviates symptoms of nicotine withdrawal or neuroleptic-induced side effects (Dalack and Meador-Woodruff 1996; Dalack et al. 1999; Decina et al. 1990; Goff et al. 1992).

Smoking may be also an attempt to improve sensory gating (Taiminen et al. 1998; Nomikos et al. 2000; Adler et al. 1993), an elementary deficit that has been observed clinically in people with schizophrenia as the inability to filter or gate their response to sensory stimuli (Venables 1967). This "flooding" has been modeled in the laboratory physiologically by measuring the amplitude of the evoked responses to identical paired auditory stimuli separated by 500 ms. The P50 auditory-evoked response occurs 40–75 ms after the presentation of a brief click. This auditory-evoked response is called the "conditioning" response. On the presentation of the second "test" stimulus, inhibitory mechanisms are normally activated so the brain can tune out repetitive nonessential noise. This gating process results in diminished amplitude of the P50 component of the evoked response to the second stimulus relative to the first. Persons with schizophrenia generally show less ability to inhibit or filter out these extraneous second stimuli, as demonstrated by a larger response to the second "test" stimulus, and a larger test wave when compared to the conditioning wave (Boutros et al. 1991; Judd et al. 1992; Ward et al. 1996; Clementz et al. 1997). This deficit is correlated with impairment in sustained attention as measured by diminished performance on the Digit Vigilance Test (Cullum et al. 1993).

2 The Mechanism of Effects of Nicotine in Schizophrenia

In animal models of this evoked potential response, cholinergic stimulation of α7 nicotinic acetylcholine receptors, which are found on presynaptic and postsynaptic sites on inhibitory interneurons of the hippocampus, is essential for this inhibition (Luntz-Leybman et al. 1992; Frazier et al. 1998; Alkondon et al. 2000). A similar deficit in auditory gating has been found in inbred mice. The DBA/2 genetic strain exhibits a failure to suppress its response to the second stimulus in a paradigm identical to that used with humans, while the C3H genetic strain shows a pattern comparable to normal humans (Stevens et al. 1996). High doses of nicotine significantly improve P50 inhibition in patients (Adler et al. 1993). When people with schizophrenia who have been withdrawn from nicotine smoke cigarettes, they are able to temporarily filter stimuli. However within approximately 30 min, their inhibitory deficit returns. Higher nicotine levels are consistent with activity at α7 receptors, which are less sensitive to nicotine than α4β2 nicotinic receptors, the other common neuronal nicotinic receptor that is found on presynaptic terminals of many different neuronal types. Longer lasting effects are not seen with the trans-dermal patch, demonstrating that prolonged effects cannot be obtained with this method of administration because of tachyphylaxis (Griffith et al. 1998). P50 abnormalities are less pronounced among schizophrenia patients who are current cigarette smokers than those who are nonsmokers, suggesting a positive effect of chronic cigarette smoking on ameliorating this inhibitory deficit (Chen et al. 2011). Studies have shown that the auditory gating improves in the DBA/2 mouse with nicotine administration (Stevens et al. 1996), just as it does in schizophrenia patients. The mechanism of auditory gating has been clarified through the use of these animal models. The activation of the α7 cholinoreceptors releases GABA from GABAergic interneurons (Albuquerque et al. 1998; Frazier et al. 1998), which then act on $GABA_B$ receptors which decreases the release of glutamate, thus preventing hippocampal neurons from responding to the second stimulus in the P50 paradigm (Hershman et al. 1995). Nitric oxide acts as a second messenger to prolong the effect of the α7 nicotinic cholinoceptor stimulation. Abnormal auditory-evoked potentials are also present in first degree relatives of people with schizophrenia even without the confounds of the pathology of the disease or the consequences of medications or chronic smoking (Siegal et al. 1984; Waldo et al. 1991;

Clementz et al. 1998; Ross et al. 1999). This finding suggests that the inhibitory deficits may be inherited.

Prepulse inhibition (PPI) is another gating deficit that is abnormal in schizophrenia. PPI refers to a reduction in response to a strong startling stimulus if preceded shortly by a stimulus of subthreshold intensity. The person is exposed to weak stimuli across a range of intensities consisting of 20–40 ms noise bursts that are typically 2–16 dB over a 70-dB noise background (prepulse), and one startling stimulus usually consisting of a 40-ms noise burst 45 dB over a 70-dB noise background. The eyeblink response to startle is measured. Deficient PPI was first reported in schizophrenia patients byBraff et al. (1978) and by several other groups subsequently (Braff et al. 2001). Nicotine administered subcutaneously or via cigarette smoking enhances PPI in healthy human beings (Kumari et al. 1997). The influence of smoking on PPI of the acoustic startle response has been examined in patients with chronic schizophrenia using cigarette smoking after abstinence (George et al. 2006; Postma et al. 2006) and nicotine nasal spray (Hong et al. 2008). The results showed a significant main effect of the drug on PPI in that nicotine improved PPI compared to placebo with no drug by diagnosis interaction. Improvement in PPI in response to nicotine was robustly correlated with the baseline severity of clinical symptoms in patients.

The mechanism of the effect on PPI has been investigated further in animal models using both rats and mice (Geyer et al. 2001, 2002). For example, in a study of nicotine effects, investigators used startle stimuli of 120 dB and prepulse intensities of 3, 6, and 12 dB above a background of 70 dB in rats and two strains of mice. In Sprague–Dawley rats, nicotine disrupted PPI and this effect was mimicked by the potent nAChR agonist, epibatidine, and the potent, and relatively selective, α4/β2 nAChR agonist A-85380 (Schreiber et al. 2002). The effects of epibatidine, A-85380, and, to a lesser extent, nicotine were blocked by the nonselective nAChR antagonist mecamylamine. The relatively selective α7 nAChR agonists, GTS-21 and AR-R-17779, did not affect PPI in a consistent manner, both in rats and in DBA/2 mice, a strain expressing a disrupted gating phenotype, presumably due to altered activity of hippocampal α7 nAChRs. In BALB/c mice, a strain expressing a normal gating phenotype, nicotine, epibatidine, and A-85380 predominantly augmented PPI and mecamylamine attenuated these effects (Schreiber et al. 2002). The results indicated that the effects of nAChR agonists on PPI are species dependent and suggest that stimulation of heteromeric nAChRs containing both α and β subunits, and possibly of the α4/β2 type, affects sensori-motor gating. Relatively selective α7 agonists do not affect PPI in a consistent manner; thus it appears that a role for α7 nAChRs in the control of PPI of the acoustic startle response is unlikely (Schreiber et al. 2002).

A third preattentive auditory sensory processing deficit that is diminished in schizophrenia patients is mismatch negativity (MMN), a negative scalp potential produced by a deviant stimulus in a series of standard stimuli. The MMN in healthy controls and patients is increased by acute administration of nicotine (Dulude et al. 2010). Twelve smoking schizophrenia subjects and 12 smoking controls were abstinent of tobacco for 3 h and then MMN was recorded in two auditory oddball paradigms, one involving tone frequency changes (frequency MMN) and one involving tone duration changes (duration MMN). Controls were assessed once under nontreatment conditions, and patients were assessed twice under randomized double-blind treatment conditions involving placebo and nicotine (8 mg) gum. In addition to prolonging peak latency in duration MMN, nicotine, relative to placebo, increased the amplitude of the patients' duration MMN, but not their frequency MMN, to a level comparable with that seen in the controls (Dulude et al. 2010). This finding suggests that acute nicotine can normalize temporal aspects of sensory memory processing in patients with schizophrenia, an effect that may be mediated by activation of α7 nicotinic acetylcholine receptors, the function of which is diminished in schizophrenia.

3 Molecular Studies of Nicotinic Receptors in Schizophrenia

Additional independent evidence for involvement of the α7 receptor in the P50 auditory-evoked potential deficit is provided through genetic studies. Nine multiplex families with schizophrenia were studied in a genome-wide linkage analysis (Freedman et al. 1997). Maximal linkage to the P50 deficit was found at chromosome 15q14 at a polymorphic marker <120 kb from the α7 gene with a LOD score of 5.3, Θ = 0.039. Linkage of this region to schizophrenia was further replicated in families from the NIMH Schizophrenia Genetics Initiative (Leonard et al. 1998) and in other studies (Riley et al. 2000; Tsuang et al. 2001; Liu et al. 2001; Xu et al. 2001), but there have also been some negative studies in this region (Neves-Pereira et al. 1998; Curtis et al. 1999). Multiple single nucleotide polymorphisms (SNP) have been identified in the 15q14 gene promoter region that are more frequently present in people with schizophrenia and their family members than normal controls (Leonard et al. 2002; Houy et al. 2004). Furthermore, the presence of a SNP in the 15q14 gene CHRNA7 5′ core promoter is significantly associated with P50 suppression deficits (Leonard et al. 2002). Association of CHRNA7 polymorphisms with P50 gating has been replicated, but the specific allelic associations differ, which suggests that responsible mutations have not yet been unambiguously identified (Leonard et al. 2002; Houy et al. 2004).

In addition to the deficits in P50-evoked potentials and the functional promoter polymorphisms in the CHRNA7 region, people with schizophrenia also have abnormalities in expression and regulation of central nicotinic cholinoceptors. Decreased α7 nicotinic cholinoceptor binding has been noted in the reticular nucleus of the thalamus, the hippocampus, the cingulate cortex, and the frontal lobe regions (Court et al. 1993; Freedman et al. 1995; Marutle et al. 2001; Guan et al. 1999). The structure of the receptor is intact in most patients with schizophrenia, but the number of receptors is diminished. These abnormalities in regulation and expression of the nicotinic cholinoreceptor may have effects on other electrophysiological and neuropsychological processes in schizophrenia.

PPI is another endophenotype that has been used to examine the involvement of the nicotinic receptor in schizophrenia. In two independent samples of 107 healthy British volunteers and 73 schizophrenia patients hailing from Germany, two common CHRNA3 polymorphisms (rs1051730/rs1317286) were examined for their effects in PPI, startle reactivity, and habituation. In both samples, PPI was influenced by both CHRNA3 polymorphisms, which were strongly linked. Moreover, CHRNA3 genotype was associated with chronicity, treatment, and negative symptoms in the schizophrenia sample (Petrovsky et al. 2010). Recent human genetic studies also imply that tobacco dependence is affected by polymorphisms in the α3/α5 subunits of the nAChR (CHRNA3/CHRNA5) gene cluster.

4 Neurocognitive Effects of Nicotine in Schizophrenia

Many of the neurophysiological abnormalities indicate preattentive or inhibitory abnormalities which implicate deficits in cognition. Withdrawal from nicotine in normal smokers has been shown to cause attention impairments (Hatsukami et al. 1989). Nicotine administration may just be relieving withdrawal and correcting those deficits. However, if low-dose nicotine is administered to normal non-smokers, thereby avoiding the confound of withdrawal, there is enhanced performance on the continuous performance test (CPT) with decreased errors of omission (missed targets) without an increase in errors of commission (nontarget responses) (Levin et al. 1998). The effects of nicotine on neuropsychological measures in persons with schizophrenia, compared to the effects on the electrophysiological measures, are less conclusive. With the hypothesis that nicotine may be both counteracting some of the cognitive effects of schizophrenia and the side effects of haloperidol, patients in

a double-blind study were randomly assigned low-, moderate-, and high-dose levels of haloperidol. The subjects, all smokers, came to the laboratory on four different mornings after overnight deprivation from cigarettes. In a double-blind fashion, they were administered placebo, low- (7 mg/day), medium- (14 mg/day), or high- (21 mg/day) dose nicotine skin patches. Three hours after administration of the skin patch, the subjects were given a computerized cognitive test battery including simple reaction time (RT), complex RT (spatial rotation), delayed matching to sample, the Sternberg memory test, and the Conners' CPT. With the placebo nicotine patch, there was a haloperidol dose-related impairment in delayed matching to sample choice accuracy and an increase in response time on the complex RT task. Nicotine caused a dose-related reversal of the haloperidol-induced impairments in memory performance and complex RT. In the CPT, nicotine reduced the variability in response that is associated with attentional deficit. These results demonstrate the effects of nicotine in reversing some of the adverse side effects of haloperidol and improving cognitive performance in schizophrenia (Levin et al. 1996). However, some may argue that nicotine is just relieving deficits that are observed in working memory that result from abstinence (Georgette et al. 2002; Sacco et al. 2005). If nicotine is then reinitiated, working memory deficits are normalized (Sacco et al. 2005).AhnAllen et al. (2008) attempted to address this issue by studying three nicotine conditions: baseline, 8 h overnight withdrawal, and 3 h 21 mg nicotine patch while performing the Attention Network Test (ANT) in 38 male cigarette smokers (22 schizophrenia, 16 normal control) matched on nicotine dependence. The results indicated that the groups did not differ in performance on either of three ANT measures (alertness, orienting, and executive) across baseline, patch, and withdrawal conditions. However, in comparison to the controls, the participants with schizophrenia showed faster ANT RT for the nicotine patch in relation to the baseline condition. In comparison to controls, the participants with schizophrenia also showed reduced ANT accuracy at withdrawal but not at patch condition. These results suggest that overall processing speed and accuracy are affected differently by nicotine levels in participants with schizophrenia, with evidence supporting greater impairment from withdrawal and greater improvement from nicotine administration. In another study, the nicotine patch also improved auditory working memory, attention, and complex RTs but not simple RTs (Sacco et al. 2005; Dépatie et al. 2002).Barr et al. (2008) found that a 14 mg patch significantly improved the performance on the CPT-identical pairs (IP) as measured by hit RT, hit RT variability, and random errors in both schizophrenia and control nonsmoker groups. In addition, nicotine reduced commission errors on the CPT-IP and improved the performance on a Card Stroop task to a greater extent in those with schizophrenia vs. controls and had more rapid and accurate recognition of novel items on a test of episodic memory (Jubelt et al. 2008).

Nicotine gum administration shows mixed effects depending on the psychological realm and whether the subjects are smokers or are nonsmokers. While nicotine gum improves attention in nonsmokers, it may diminish attention in smokers. In contrast, nicotine gum has no effect in either smokers or nonsmokers on working memory or visuospatial memory (Harris et al. 2004). Finally, nicotine nasal spray had variable effects on verbal (Kem et al. 1971, 1997) spatial working memory (Smith et al. 2002, 2006) and complex RTs but had no effect on simple RT attention or working memory (Levin et al. 1996; Sherr et al. 2002; Myers et al. 2004). Thus, chronic exposure to nicotine in smokers, the mode of experimental nicotine delivery, the nicotine dose given, the particular neuropsychological test, clinical diversity, and potentially other factors in these studies may account for the variability of these findings. Nicotine has several limitations as a therapeutic agent for schizophrenia. Nicotine induces tachyphylaxis and thus does not maintain sustained benefit because of receptor desensitization. Additionally, the long-term health risks of chronic nicotine use are unknown. Nicotine is also addictive and without sustained use, people can experience

symptoms of withdrawal (Benowitz 1998). Thus, alternative nicotinic agonists that are less potentially toxic would be helpful in the treatment of schizophrenia.

One of the few nicotinic agents that has reached clinical trials is GTS-21 or 3-[2,4-dimethoxybenzylidene]anabaseine (DMXB-A). DMXB-A (Kem et al. 1971, 1997) is a derivative of the naturally occurring alkaloid anabaseine (Kem et al. 2004). It is a partial agonist at human α7 nicotinic receptors and at higher concentrations a weak antagonist at α4β2 receptors and serotonin 5-HT_3 receptors (Kem et al. 2004; De Fiebre et al. 1995; Briggs et al. 1995; Stokes et al. 2004). Approximately 40% of an oral dose is absorbed within 1 h of administration (Mahnir et al. 1998). Metabolites with hydroxyl substituents at positions 2 and 4 are more efficacious agonists when bound to the receptor, but to what extent they are produced in human brain is unknown (Stokes et al. 2004; Mahnir et al. 1998). DMXB-A improves memory in several animal models, and it normalizes inhibition of auditory responses in rodents, with significantly less tachyphylaxis than nicotine (Woodruff-Pak et al. 1994; Stevens et al. 1998). The first step in testing of this compound was to administer DMXB-A subcutaneously in DBA/2 mice. This compound produced a dose-dependent improvement in auditory gating that occurred through a selective reduction in the response to the second stimulus. The improvement in auditory gating has been replicated in isolation-reared rats which show deficient auditory gating (O'Neill et al. 2003), in C3H mouse strains chronically treated with cocaine, which also show deficient auditory gating (Stevens et al. 1999), and after oral administration of DMXB-A in DBA/2 mice (Simosky et al. 2001). DMXB-A improves many of the neurophysiological abnormalities in schizophrenia models in animals that are corrected by nicotine. Administration of DMXB-A also improves deficient PPI (Schreiber et al. 2002).

DMXB-A improves monkey performance on a delayed matching to sample task, an effect that persists for 24 h after drug administration (Briggs et al. 1997). The administration of DMXB-A improves eyeblink classical conditioning acquisition in older rabbits who have lost cholinergic neurons (Woodruff-Pak et al. 1994). Mecamylamine, an α4β2 antagonist, has a deleterious effect on conditioned learning in young rabbits. If young rabbits are given mecamylamine and DMXB-A, their eyeblink classical conditioning acquisition is improved (Woodruff-Pak 2003). DMXB-A improves one-way active avoidance, Lashley III maze testing, and 17-arm radial maze test performance in aged rats (Arendash et al. 1995; Meyer et al. 1998). Passive avoidance deficits are normalized in rats (Meyer et al. 1994) and ischemia-induced hippocampal cell death and impaired passive avoidance performance in gerbils are prevented by treatment with DMXB-A (Nanri et al. 1998). DMXB-A also improves performance on the Morris water maze (Meyer et al. 1997).

Positive neurocognitive effects, particularly on attention, were observed in healthy volunteers when administered DMXB-A (Kitagawa et al. 2003). The first stage in human testing with DMXB-A was to initially administer this compound to normal male subjects (n = 18) to assess for safety, tolerability, pharmacokinetics, and possible effects on cognition prior to its study as a cognitive enhancer in Alzheimer's disease (Kitagawa et al. 2003). Subjects were randomized to DMXB-A (25, 75, and 150 mg) or placebo administered three times daily for 5 days with a 10 day washout period between drug-taking periods. All subjects were evaluated for performance on a computerized test battery to measure the effect of treatment on cognitive functioning including changes in attention (simple RT, choice RT, digit vigilance), numeric and spatial working memory, secondary episodic recognition memory (word and picture recognition, immediate and delayed word recall), and visual tracking. Peak plasma levels were achieved at 1–1.4 h after the first dose and 1–1.2 h after 5 days of dosing. DMXB-A was well tolerated at doses of up to 450 mg daily with no significant safety findings. DMXB-A significantly improved performance on simple RT, choice RT, correct detection during digit vigilance, both word and picture recognition

memory, and both immediate and delayed word recall. Additionally, DMXB-A improved subject performance speed on numeric and spatial working memory task. Improvement was generally seen with the 25 mg dose, with further improvement at the 75 mg dose and an equivalent effect at the 150 mg dose (Kitagawa et al. 2003).

5 Initial Trials of Nicotinic Agonists in Schizophrenia

In an initial trial in schizophrenia, DMXB-A was given in a 1 day administration to determine if the drug was safe and to obtain a proof-of-principle preliminary indication of efficacy by improving neurocognition and assessing its effects on P50 inhibition to see if its actions are consistent with activation of α7 nicotinic receptors (Olincy et al. 2006). Because the proposed effect is agonism at a ligand-gated ion channel, biological effects were expected immediately, consistent with the results from animal models. DMXB-A was administered orally (150 mg or 75 mg) followed 2 h later by a supplemental half dose (75 mg or 37.5 mg). The half dose, administered at the predicted half-life of the first dose, extended the period of therapeutic drug levels during the behavioral measurements. Twelve nonsmoking schizophrenia subjects received either the higher or lower dose or placebo in a double-blind, three-arm, random order crossover with the study drug or placebo added on to their current antipsychotic regimen.

The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) was administered immediately following the second dose on each experimental day (Gold et al. 1999). The primary neurophysiological measure was P50 auditory-evoked potential suppression in response to repeated stimuli (Adler et al. 1993). This measure was chosen because it had previously demonstrated effects of nicotinic agonism in schizophrenia and effects of DMXB-A in animal models (Adler et al. 1993; Stevens et al. 1998). DMXB-A in plasma was quantitatively determined by a modification of previously reported HPLC methods (Mahnir et al. 1998). The plasma concentrations were consistent with the pharmacokinetic parameters established in the previous Phase 1 study in healthy controls.

P50 suppression was measured before drug administration on each day; these baseline values were not significantly different, consistent with the lack of repetition effects on this measure. The amplitude of the P50 response to the conditioning stimulus was not significantly different over the three treatment conditions. However, the amplitude of the second or test response and the P50 test/conditioning ratio were significantly decreased during low dose compared to placebo. The neurocognitive effect of drug treatment as measured by the RBANS Total Scale score at the 150 mg dose was significant for the effect of treatment.

Based on the results of the Phase 1 trial, the Phase 2 trial was approved by the FDA to assess whether cognitive effects would continue during longer term administration and whether clinical ratings would also change (Freedman et al. 2008). The doses were those used in the Phase 1 trial. The MATRICS Battery was chosen because of its recommended use for assessment of drug effects on cognition in schizophrenia (Nuechterlein et al. 2008; Kern et al. 2008). Standard clinical measures, the Scale for Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS), were also assessed. As in the initial Phase 1 trial, clinically stable nonsmoking patients, almost all of whom were currently taking antipsychotic drugs, were studied.

Thirty-one subjects were enrolled at two sites. Subjects were assigned to 4 weeks of placebo bid, 75 mg bid DMXB-A, or 150 mg bid DMXB-A in a double-blind balanced crossover design.

Performance on the six domains of the MATRICS CCB did not differ between DMXB-A dosage and placebo, and effects of repetition of the tests were observed in several of the domains.

Therefore, a secondary analysis was performed using only the results of the first arm of the study, to minimize the effects of repetition of the tests. Two domains showed significant improvement over baseline with DMXB-A treatment in the first arm. The Attention Vigilance domain T score showed no significant change over baseline with placebo, but it showed significant change with 75 mg bid DMXB-A and with 150 mg bid DMXB-A. The Working Memory domain T score also showed no significant change over baseline with placebo, but it showed significant change with 75 mg bid DMXB-A and a trend with 150 mg bid DMXB-A (Freedman et al. 2008). Significant effects of DMXB-A treatment were observed for the SANS total score at 150 mg bid. Two of the subscales, Alogia and Anhedonia, showed significant effects of 150 mg bid DMXB-A, compared to placebo.

Additionally, subjects during each arm of treatment participated in a default mode fMRI task. Both 150 mg and 75 mg DMXB-A were associated with less default network activity in the posterior cingulate, inferior parietal cortex, and medial frontal gyrus when compared to placebo. The opposite response, greater default mode activity associated with drug, was observed in the precuneus. Decreases in posterior cingulate default network activity were positively correlated with decreases in total BPRS score. Increases in precuneus default network activity were significantly correlated with decreases in SANS total score (Tregellas et al. 2011).

Not only does DMXB-A apparently at both 75 and 150 mg appear to reduce default network activity, there also appears to be a pharmacogenomic effect related to the *CHRNA7* allelic variant. The *CHRNA7* allelic variant chosen for initial study of pharmacogenomic effects was rs3087454, located 1,831 bp 5′ of Exon 1 in the promoter region of the α7 nicotinic receptor gene on 15q13-14. SNP rs3087454 is associated with schizophrenia (Stephens 2009). Its location is within the chromosome 15q13-14 region found to be deleted in rare cases of schizophrenia occurring after small de novo chromosomal deletions (Stone et al. 2008). The polymorphism occurs very frequently with a set of polymorphisms in the core promoter that decrease its function as assessed in vitro (Leonard 2002). Thus, the polymorphism is associated with both the function of the *CHRNA7* gene to produce α7 nAChRs and the genetic risk for schizophrenia. Our initial pharmacogenomic study of this SNP was conducted in the Phase 1 study of DMXB-A in schizophrenia. The minor allele that is associated with schizophrenia significantly decreased the neuropsychological effect of DMXB-A. In the Phase 2 study of DMXB-A, significant genotypic effects were also observed with the minor allele being associated with decreased response to the agonist during a default network task (Tregellas et al. 2010).Liu et al. (2009) also reported similar significant genotypic effects of SNP rs3087454 on default network activity in schizophrenia. These results are consistent with the hypothesis that genetically mediated decrease in α7 nAChRs results in decreased nicotinic cholinoreceptor activation of inhibitory interneurons, as predicted from animal models. The patients thus appear to have reduced response to their endogenous acetylcholine, as well as diminished response to DMXB-A.

DMXB-A needs to be tested further in longer trials to assess this drug's potential to sustain its effects on cognition. Additionally, as the testing was in a relatively uncommon population, people with schizophrenia that are nonsmokers, to avoid interactions of nicotinic agonists with already desensitized nicotinic cholinoceptors, a trial of these types of drugs in smokers is warranted. Furthermore, the half-life of DMXB-A is relatively short (1.5 h) with a peak effect at about 2 h, requiring frequent administration and making it impractical for

use in a cognitively impaired, non-adherent population. Thus, other delivery systems or other nicotinic agonists with longer half-lives are currently in development.

Other potential α7 nicotinic agonists have been developed as potential candidates for the treatment of schizophrenia and Alzheimer's disease. Targacept, Inc. has an (E)-*N*-methyl-5 (3-pyridinyl)-4-penten-2-amine and TC-5619 *N*-[2-(pyridine-3ylmethyl)-1-azabicyclo[2.2.2]oct-3-yl]-1-benzofuran-carboxamide which binds with high affinity to the α7 subtype and is a potent full agonist (Hauser et al. 2009). TC-5619 attenuated PPI and startle in transgenic th(tk-)/th(tk-) mice and these mice spent more time investigating novel objects. In a double-blind, placebo-controlled trial TC-5619 was administered for 12 weeks to 185 outpatients with schizophrenia (Hosford et al. 2011). All subjects were taking quetiapine or risperidone. The primary outcome was executive function tested at weeks 4, 8, and 12 as measured by Groton Maze Learning Task (GMLT) from the computerized Cogstate Schizophrenia battery (CSB). Secondary measures were the CSB composite score Scale of the Assessment of Negative Symptoms (SANS), CGI-Global Impression (CGI-I), CGI-Severity (CGI-S), and Subject Global Impression-Cognition (subject-rated scale assessing Speed of Thinking, Memory, and Attention). GMLT, SANS, CGI-I, and SGI-Cog results favored TC-5619. Somewhat surprisingly, the effect was primarily driven by tobacco users. There were no noteworthy safety findings.

Another potent and selective partial agonist of the α7 nicotinic acetylcholine receptor is (R)-7-chloro-*N*-(quinuclidin-3-yl)benzo(b)thiophene-2-carboxamide, EVP-6124, a compound developed by Envivo Pharmaceuticals. EVP-6124 significantly restored memory function in scopolamine-treated rats in an object recognition task (Prickaerts et al. 2012). This drug has been tested in 9 clinical studies with 403 subjects receiving EVP-6124 and 158 receiving placebo (Meltzer et al. 2011). In a Phase 2b study in participants with schizophrenia, on chronic atypical antipsychotic therapy, subjects were given one of two doses of EVP-6214 (0.3 mg or 1 mg once daily) or placebo for 84 days. Efficacy was evaluated using the Overall Cognition Index (OCI) from the Cogstate testing battery and Trails 2 and 4 of the Neuropsychological Test Battery (NTB), the MATRICS Consensus Cognitive Battery (MCCB), the Schizophrenia Cognition Rating Scale (SCoRS), and the positive and negative syndrome scale (PANSS). The OCI plus Trails 2 and 4 suggested that 0.3 mg of EVP-6124, compared to placebo, was associated with improvement in general cognitive function and that this effect was mainly due to beneficial effects on visual learning, visual attention, and social cognition. Significant effects in clinical function were also seen with EVP-6124 treatment as measured by the SCoRS Interviewer Rating of clinical function. Improvement was also seen in the negative symptoms of schizophrenia (derived from the PANSS) with mean decreases greater in the 1 mg of EVP-6124 compared to the placebo group. The drug was well tolerated with no significant changes in ECG's vital signs, hematology, serum chemistry, or suicidal ideation. The most commonly reported adverse events were headache (3.8%), nausea (3.2%), and nasopharyngitis (2.5%), and no serious adverse event was judged as related to the drug.

Notable differences between TC-5619, EVP-6124, and DMXB-A include the longer half-life of TC-5619 (24 h) and EVP-6214 (>60 h) compared to 1.5 h for DMXB-A (Hosford et al. 2011; Meltzer et al. 2011). This difference suggests that TC-5619 and perhaps other α7 nicotinic agonists will not show the tachyphylaxis that might have been expected with nicotinic receptor activation. TC-5619 was also more effective in smokers than in nonsmokers; DMXB-A has not been tested in smokers. This observation also suggests that tachyphylaxis might not be problematic with this approach to nicotinic receptor activation.

Other drugs currently in development include 4-(5methyloxazolo[4,5-b] pyrudub-2yl)-1,4-diazabicyclo[3.2.2]nonane (Compound 24). This is a potent and selective agonist with high

oral bioavailability and in vivo efficacy in auditory sensory gating and novel object recognition (O'Donnell et al. 2010). Pfizer currently has two drugs in development. They include a 1,4-diazabicyclo[3.2.2] nonane-4-carboxylic acid 4-pyridin-2yl-phenyl ester and a *N*-[(3R)-1-azabicyclo [2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide (14 PHA-543,613). The second compound demonstrates reversal of amphetamine-induced N40 gating deficit in anesthetized rats and improves the ability to discriminate between familiar and novel objects (Wishka et al. 2006).

SSR180711 from Sanofi-Aventis enhances long-term memory in the object recognition task in mice and latent inhibition in rats pre-administered methyllycaconitine, an α7 nicotinic cholinoceptor antagonist. However, when administered to α7 knockout mice, there is no enhancement of long-term memory (Pichat et al. 2007; Barak et al. 2009). ABT-418 has some agonist properties at the α7 nicotinic cholinoceptors, but is a less potent agonist than nicotine with greater selectivity at α4β2 nAChRs (Briggs et al. 1995). ABT-418 restores deficient auditory gating in DBA/2 mice as well as rats with fimbria–fornix lesions (Stevens and Wear 1997). ABT-418 also improves sustained attention in poorly (McGaughy et al. 1999) but not well (Turchi et al. 1995) performing rat strains. JN403, a compound recently characterized to be a potent and selective partial α7 nAChR agonist, rapidly penetrates into the brain after i.v. and after p.o. administration in mice and rats. In the social recognition test in mice JN403 facilitates learning/memory performance over a broad dose range. Systemic administration of JN403 restores sensory gating in DBA/2 mice, both in anesthetized and awake animals (Feuerbach et al. 2009). AstraZeneca has AZD0328 ((2′R)-spiro-[1-azabicyclo[2.2.2]octane-3,2′ (3′H)-furo[2-3-b]p[pyridine] p-tartrate), a neuronal nicotinic partial agonist. Mice treated with AZD0328 increased novel object interaction relative to vehicle and had successful acquisition of reinforced tasks (Sydserff et al. 2009). Roche/Memory R3487/MEM3454, an α7 receptor partial agonist with $5HT_3$ antagonist properties, has improved attention and working memory performance in cynomolgus macaques (Wallace et al. 2009).

Several positive allosteric modulators of the α7 nicotinic acetylcholine receptor have also been developed. Johnson & Johnson has JNJ-1930942 which enhances a choline-evoked rise in intracellular calcium but does not act on α4β2, α3β4, or $5HT_3$ channel. This agent improves the auditory gating deficit in DBA/2 mice (Lesage et al. 2009). Abbott has A-716096 which also improved sensory gating in DBA/2 mice (Donnelly-Roberts et al. 2009). 1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methyl-isoxazol-3-yl)-urea (PNU-120596) is another agent which acts as a powerful positive allosteric modulator of the α7 nAChR and was discovered in high-throughput screen. This compound produces no detectable change in currents mediated by α4β2, α3β4, and α9α10 nAChRs; however, it increases the channel mean open time of α7 nAChRs. When applied to acute hippocampal slices, PNU-120596 increased the frequency of ACh-evoked GABAergic postsynaptic currents measured in pyramidal neurons; this effect was suppressed by TTX, suggesting that PNU-120596 modulated the function of α7 nAChRs located on the somatodendritic membrane of hippocampal interneurons. Systemic administration of PNU-120596 to rats improved the auditory gating deficit caused by amphetamine, a model proposed to reflect a circuit level disturbance associated with schizophrenia (Hurst et al. 2005).

6 Other Therapeutic Approaches Targeting Nicotinic Receptors

Other compounds currently in clinical use that have direct or indirect effects on α7 nicotinic receptors. Galantamine, an acetylcholinesterase inhibitor, an allosteric modulator of several nicotinic receptors including the α7 nicotinic receptor, improved several aspects of cognition in schizophrenia and also improved the SANS Alogia score (Buchanan et al. 2008). In contrast, rivastigmine, which does not have these allosteric properties, had no

effect in schizophrenia (Sharma et al. 2006). Varenicline, possessing partial agonism at the α4β2 nicotinic receptor, full agonism at the α7 nicotinic receptor, and also weak activity at α3β4 and α6 receptors, has been tested in 14 schizophrenic smokers in an open-label with a pre-post design. Measures of cognitive function (RBANS, Virtual Water-Maze Task), cigarette smoking (cotinine levels, CO levels, self-reported smoking, and smoking urges), and psychopathology (PANSS) were evaluated prior to and during treatment with varenicline. Data on psychopathology changes among schizophrenic smokers in another drug study, in which patients were not receiving varenicline, were used for comparison. Twelve patients completed the study, and two patients terminated in the first 2 weeks of active varenicline because of complaints of nausea or shaking. Varenicline produced significant improvements in some cognitive test scores, primarily associated with verbal learning and memory, but not in scores on visual–spatial learning or memory, or attention (Smith et al. 2009). A second double-blind, parallel, randomized, placebo-controlled trial of 69 smoking and nonsmoking patients with schizophrenia or schizoaffective disorder examined the effects of varenicline on PPI, sensory gating, antisaccade, spatial working memory, eye tracking, processing speed, and sustained attention at 2 and 8 weeks. A moderate dose (1 mg) of varenicline significantly reduced the P50 sensory gating deficit in nonsmokers after 8 weeks of treatment, reduced startle reactivity regardless of baseline smoking status, and improved executive function by reducing the antisaccadic error rate regardless of smoking status. A moderate dose of varenicline had no significant effect on spatial working memory, predictive and maintenance pursuit measures, processing speed, or sustained attention by Conners' CPT. Clinically, there was no evidence of exacerbation of psychiatric symptoms, psychosis, depression, or suicidality using a gradual titration (1-mg daily dose). Moderate-dose treatment with varenicline has a unique treatment profile on core schizophrenia-related biomarkers. Further development is warranted for specific nAChR compounds and dosing and duration strategies to target subgroups of schizophrenic patients with specific biological deficits.

Tropisetron, also a $5HT_3$ antagonist marketed outside the United States as an antinausea drug, also has efficacy as an α7 nicotinic cholinoceptor agonist (Macor et al. 2001; Papke et al. 2005). Low-dose single administration of tropisetron increased the inhibition of the P50 auditory-evoked potential differentially in nonsmokers with schizophrenia (Koike et al. 2005) with no effect seen on smokers with schizophrenia. Consistent with a previous finding of the effect in smokers (Harris et al. 2004), the authors proposed that the nicotinic cholinoceptors were chronically densensitized and that additional nicotinic agonism was blocked in smokers. The finding was recently replicated byKosten et al. (2011). Kosten also found that tropisetron administered to patients with schizophrenia normalized their P50 gating deficit. The effects were diminished in patients who smoked.

The most important drug with indirect effects on α7 nicotinic receptor is clozapine. People with schizophrenia treated with clozapine exhibit normalization of their P50 ratio coincident with improvement in their clinical symptoms (Nagamoto et al. 1999; Becker et al. 2004). Clozapine, which releases acetylcholine in the hippocampus (Shirazi-Southall et al. 2002), may indirectly act on the nicotinic cholinoceptors to normalize the P50 ratio, as people with schizophrenia also decrease the amount of cigarettes they smoke while taking this medication (McEvoy et al. 1999; Becker et al. 2004). Animal model experiments also show that the neurobiological effects of clozapine include activation of α7 nicotinic receptors, presumably through the increased release of acetylcholine in the hippocampus. The gating deficit in the DBA/2 mouse normalized with clozapine (Simosky et al. 2003). The response to clozapine was blocked by α-bungarotoxin, a selective antagonist at the α7 nicotinic receptor, but not by dihydro-beta-erythroidine (DHbetaE), an α4β2 antagonist, thus indicating the involvement of the low-affinity nicotinic receptors (Simosky et al. 2003).

7 Conclusion

Both basic and clinical evidence points to the possibility that nicotinic receptors, particularly the α7 nicotinic receptor, are viable targets for drug development in schizophrenia. Several partial agonists have shown positive effects, which surpass those of nicotine. Development of other therapeutic approaches, including positive allosteric modulators, is under way. To what extent nicotinic receptor activation accounts for the unique therapeutic effects of clozapine is unknown, but it is striking that many patients stop smoking when they are successfully treated with clozapine. Unanswered questions include long-term toxicity and tachyphylaxis, both of which have been observed with nicotinic agonists, and the ability of these agents to be effective in the presence of nicotine from the patients' own smoking.

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