

# SCHIZOPHRENIA AND THE $\alpha 7$ NICOTINIC ACETYLCHOLINE RECEPTOR

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In addition to the devastating symptoms of psychosis, many people with schizophrenia also suffer from cognitive impairment. These cognitive symptoms lead to marked dysfunction and can impact employability, treatment adherence, and social skills. Deficits in P50 auditory gating are associated with attentional impairment and may contribute to cognitive symptoms and perceptual disturbances. This nicotinic cholinergic-mediated inhibitory process represents a potential new target for therapeutic intervention in schizophrenia. This chapter will review evidence implicating the nicotinic cholinergic, and specifically, the  $\alpha 7$  nicotinic receptor system in the pathology of schizophrenia. Impaired auditory sensory gating has been linked to the  $\alpha 7$  nicotinic receptor gene on the chromosome 15q14 locus. A majority of persons with schizophrenia are heavy smokers. Although nicotine can acutely reverse diminished auditory sensory gating in people with schizophrenia, this effect is lost on a chronic basis due to receptor desensitization. The  $\alpha 7$  nicotinic agonist 3-(2,4 dimethoxy)benzylidene-anabaseine (DMXBA) can also enhance auditory sensory gating in animal models. DMXBA is well tolerated in humans and a new study in persons with schizophrenia has found that DMXBA enhances both P50 auditory gating and cognition.  $\alpha 7$  Nicotinic acetylcholine receptor agonists appear to be viable candidates for the treatment of cognitive disturbances in schizophrenia.

## I. Introduction

In addition to the more obvious symptoms of hallucinations and delusions, people with schizophrenia frequently suffer from cognitive symptoms such as the inability to focus attention. This results in a “flooding” with extraneous sensory stimuli which overwhelms the person’s ability to think coherently (Venables, 1992). Poor cognitive functioning contributes to both poor role-functioning and high costs of care through its association with activities of daily living, productivity, rate of inpatient hospitalization and outpatient utilization, independence, trainability/education levels, employability, and the lost productivity of family members spent caring for their ill relatives (reviewed in Sevy and Davidson, 1995). Cognitive impairment also contributes to poor medication adherence (Jeste *et al.*, 2003) and limits the efficacy of rehabilitative therapies (reviewed in Sharma and Antonova, 2003). Cognitive deficits improve slightly with current antipsychotic medications, but they are not normalized and therefore remain a target for new treatment efforts (Weickert *et al.*, 2003). Given increasing evidence for a role of the nicotinic cholinergic system’s role in the cognitive symptoms of schizophrenia, the  $\alpha 7$  nicotinic acetylcholine receptor has been proposed as a candidate for the development of medications specifically targeting cognitive deficits in schizophrenia (Martin *et al.*, 2004). This chapter will review the neurobiological findings that led to the development of this promising new drug treatment for schizophrenia as well as new evidence for the beneficial effect of an  $\alpha 7$  nicotinic receptor agonist on cognitive impairment in schizophrenia.

## II. Neurobiological and Neurogenetic Evidence for a Link Between the $\alpha 7$ Nicotinic Acetylcholine Receptor and Schizophrenia

Sensory gating, measured using the P50 auditory-evoked response, is impaired in persons with schizophrenia (Adler *et al.*, 1985). The P50 auditory-evoked response occurs 40–75 ms following an auditory stimulus. When a second auditory stimulus is presented in close proximity (500 ms), the P50 auditory-evoked response to the second stimulus is diminished, which is evidence for the activity of an inhibitory process. This impairment has been replicated in multiple independent laboratories (Boutros *et al.*, 1991; Clementz *et al.*, 1997; Judd *et al.*, 1992; Louchart-de la Chapelle *et al.*, 2005; Ward *et al.*, 1996) and is present by the first episode of psychosis (Yee *et al.*, 1998). This inhibitory failure is associated with poor sustained attention, as measured by diminished performance on the Digit Vigilance Test and other tests of attentional dysfunction (Cullum *et al.*, 1993; Yee *et al.*, 1998).

Evidence for the role of the  $\alpha 7$  nicotinic acetylcholine receptor in auditory gating was initially established using multiple animal models. The auditory-evoked response of hippocampal CA3 pyramidal neurons in the rat, the P20-N40 field potential, parallels the properties of the human P50 auditory-evoked response. The  $\alpha 7$  nicotinic receptor antagonist  $\alpha$ -bungarotoxin disrupts P20-N40 gating, while the nicotinic receptor channel blocker mecamylamine and the muscarinic antagonist scopolamine have no effect on P20-N40 gating (Luntz-Leybman *et al.*, 1992). The DBA/2 strain of mice has genetically decreased levels of  $\alpha 7$  nicotinic receptors in the CA3 region and impaired auditory gating (Stevens *et al.*, 1996). Finally, nicotine restores auditory gating in fimbria-fornix lesioned rats with impaired auditory gating due to the loss of cholinergic innervation to the hippocampus (Bickford and Wear, 1995).

$\alpha 7$  Nicotinic receptors mediate this inhibitory processing by enhancing the release of gamma-aminobutyric acid (GABA) from GABAergic interneurons via a postsynaptic, calcium-dependent mechanism (Albuquerque *et al.*, 1998; Frazier *et al.*, 1998). Nitric oxide prolongs this effect through a second messenger system (Adams *et al.*, 2000). This enhanced release of GABA stimulates GABA<sub>B</sub> receptors which in turn decreases the release of glutamate (Hershman *et al.*, 1995). This effect is thought to prevent hippocampal neurons from responding to the second stimulus in the auditory gating paradigm. These nicotinic receptor-mediated interactions between inhibitory (GABA) and excitatory (glutamate) neurons are also proposed to play a role in the efficiency and patterning of neuronal functioning within the hippocampus and cortex (Albuquerque *et al.*, 2000; Alkondon *et al.*, 2000; Ji and Dani, 2000; Jones *et al.*, 1999).

A parallel series of studies in humans also implicated the  $\alpha 7$  nicotinic acetylcholine receptor in the physiology of P50 auditory gating. Nicotine gum and physostigmine were found to improve gating in the relatives of persons with schizophrenia who also had impaired auditory gating (Adler *et al.*, 1992). The study of this group of relatives was especially useful as it was able to avoid the confounds of the additional pathological effects of schizophrenia, the effects of chronic neuroleptic treatment as well as the effects of chronic smoking on nicotinic receptor levels. These findings were extended to persons with schizophrenia (Adler *et al.*, 1993). Next, mecamylamine was administered with nicotine at a dose which blocks  $\alpha 4/\beta 2$  receptors. Mecamylamine did not attenuate the nicotine induced enhancement of auditory gating. Therefore, the  $\alpha 7$  nicotinic receptor appears to be the primary cholinergic receptor responsible for P50 auditory gating in humans as well (Freedman *et al.*, 1994).

In addition to the  $\alpha 7$ -mediated deficits in P50 auditory gating, people with schizophrenia also have abnormalities in the expression of central nervous system nicotinic receptors. Decreased  $\alpha 7$  nicotinic receptor binding has been noted in the reticular nucleus of the thalamus (Court *et al.*, 1999), the hippocampus (Freedman *et al.*, 1995), and the cingulate cortex (Marutle *et al.*, 2001).

Reduced  $\alpha 7$  subunit levels have been noted in frontal lobe regions (Guan *et al.*, 1999), including the dorsolateral prefrontal cortex (Martín-Ruiz *et al.*, 2003). Reduced levels of mRNA are also seen in peripheral blood lymphocytes (Perl *et al.*, 2003).

The relatives of persons with schizophrenia also have poor P50 auditory gating (Clementz *et al.*, 1998; Ross *et al.*, 1999; Siegal *et al.*, 1984), consistent with a genetically determined trait (Waldo *et al.*, 1991). An initial genome scan using poor P50 auditory gating as a phenotype gave only suggestive results at several chromosomes (Coon *et al.*, 1993). Following the identification of genetic markers specific to the  $\alpha 7$  nicotinic acetylcholine receptor gene (CHRNA-7) at 15q13–14 (Chini *et al.*, 1994), P50 auditory gating was linked to the chromosome 15q14 locus of CHRNA-7 (Freedman *et al.*, 1997). Families from the NIMH Schizophrenia Genetics Initiative database have since been utilized to find linkage to the diagnosis of schizophrenia itself (Leonard *et al.*, 1998). Since that time, replications of these findings have occurred in North American families of African descent (Kaufmann *et al.*, 1998) and European descent (Tsuang *et al.*, 2001), German families (Stöber *et al.*, 2000), South African families (Riley *et al.*, 2000), Azorean families (Xu *et al.*, 2001), Taiwanese families (Liu *et al.*, 2001) and Canadian families (De Luca *et al.*, 2004). Other studies, including those that have looked specifically at this region, have not found linkage (Curtis *et al.*, 1999; Neves-Pereira *et al.*, 1998).

Although no amino acid-coding region polymorphisms have been identified, multiple single nucleotide polymorphisms in the promoter region of CHRNA-7 as well as a partial duplication of the CHRNA-7 gene have been characterized (Gault *et al.*, 1998). Certain alleles are more frequently present in people with schizophrenia and their family members (Houy *et al.*, 2004; Leonard *et al.*, 2002). Furthermore, as some of these alleles are associated with both decreased promoter region activity *in vitro* and impaired P50 auditory gating, they represent functional polymorphisms that may be related to brain inhibitory pathway failure (Leonard *et al.*, 2002).

### III. The Prototypic $\alpha 7$ Nicotinic Agonist, Nicotine, and Schizophrenia

The frequency of tobacco smoking is elevated in people with schizophrenia in both inpatient (De Leon *et al.*, 1995; Llerena *et al.*, 2003) and outpatient settings (Diwan *et al.*, 1998; Hughes *et al.*, 1986). They are heavier smokers (De Leon *et al.*, 1995; Kelly and McCreadie, 1999; Lasser *et al.*, 2000; Masterson and O'Shea, 1984) and they extract more nicotine per cigarette smoked than the general population (Olincy *et al.*, 1997; Strand and Nybäck, 2005 but see Bozikas *et al.*, 2005). In addition to the health implications of smoking (Goff *et al.*, 2005), the burden of this heavy use includes spending 27% of an already limited income on

the purchase of cigarettes (Steinberg *et al.*, 2005). Their motivation to quit smoking is low (Addington *et al.*, 1997; Ziedonis and George, 1997), and the smoking cessation rate is lower than the rates of other mentally ill populations (Diwan *et al.*, 1998) and the general population (Kelly and McCreadie, 1999). Fortunately, interventions targeted specifically for persons with schizophrenia are being developed (Steinberg *et al.*, 2004; Ziedonis *et al.*, 2003). Successful interventions have utilized cognitive behavioral therapy and sustained release bupropion (Evins *et al.*, 2001; Weiner *et al.*, 2001), nicotine replacement therapy (Breckenridge, 1990; Chou *et al.*, 2004; George *et al.*, 2000; Williams *et al.*, 2004; Ziedonis and George, 1997), cognitive behavioral therapy alone (Addington *et al.*, 1998), and contingent monetary reinforcement (Tidey *et al.*, 2002) to reduce smoking or promote abstinence. The reduction in smoking achieved may last for up to 2 years following the cessation treatment and is associated with a greater likelihood of abstaining in the future (Evins *et al.*, 2004).

The high rate and heavy level of smoking seen in this population may be related to the illness or its treatment (reviewed in Dalack *et al.*, 1998). Patients report that they smoke as a sedative, to reduce negative symptoms, and to counteract medication side effects (Forchuk *et al.*, 2002). Some investigators have hypothesized that smoking in people with schizophrenia may be their striving to reduce neuroleptic-induced side effects such as iatrogenic parkinsonism (Decina *et al.*, 1990; Goff *et al.*, 1992). Others have hypothesized that smoking may be an attempt to prevent worsening of their symptoms during nicotine withdrawal (Dalack *et al.*, 1999; Dalack and Meador-Woodruff, 1996) or an endeavor to alleviate symptoms of depression, anxiety, anhedonia, or amotivation (Glassman, 1993; Nisell *et al.*, 1995; Svensson *et al.*, 1990; Tung *et al.*, 1990). Finally, smoking may be a strategy to improve cognition (Nomikos *et al.*, 2000; Taiminen *et al.*, 1998) and sensory gating (Adler *et al.*, 1993).

Systematic studies of these hypotheses involving the administration (or withdrawal) of nicotine have demonstrated positive effects on movement disorders, negative symptoms, some cognitive tasks, sensory gating, and eye movement performance. Nicotine patch administration can improve tremor, bradykinesia-rigidity, and akathisia (Anfang and Pope, 1997; Yang *et al.*, 2002). However, one study found a worsening of Abnormal Involuntary Movement Scale scores following nicotine patch administration (Dalack *et al.*, 1999) and another study found no effect of smoking on tardive dyskinesia, extrapyramidal or parkinsonian symptoms (Smith *et al.*, 2002). Nicotine withdrawal as part of an abstinence or harm reduction treatment may exacerbate psychotic and depressive symptoms (Evins *et al.*, 2001), although this exacerbation may be prevented by the use of nicotine replacement (George *et al.*, 2000) or bupropion (Evins *et al.*, 2001; Weiner *et al.*, 2001). The use of a nicotine patch in a research setting does not affect Brief Psychiatric Rating Scale scores or Scale for the Assessment of Negative Symptoms SANS; (Dalack *et al.*, 1999; Yang *et al.*, 2002). A case report

found that adjuvant galantamine, the anticholinesterase inhibitor and allosteric nicotinic receptor modulator, improved the SANS score (Rosse and Deutsch, 2002).

The effects of nicotine on neuropsychological measures in persons with schizophrenia have been mixed. Abstinence and then reinitiation of smoking had no effect on attentional measures (Sacco *et al.*, 2005), the nicotine patch improved attention (Dépatie *et al.*, 2002; Levin *et al.*, 1996), nicotine gum worsened attention in smokers and improved it in nonsmokers (Harris *et al.*, 2004), and nicotine nasal spray had no effect on attention (Sherr *et al.*, 2002). Smoking abstinence impaired working memory (George *et al.*, 2001; Sacco *et al.*, 2005) and the reinstatement of smoking improved performance (Sacco *et al.*, 2005). The nicotine patch also improved haloperidol-induced deficits on another test of working memory (Levin *et al.*, 1996). A functional magnetic resonance imaging study of an auditory working memory task found a behavioral improvement following nicotine patch that was associated with increased activation within the insula, putamen, and thalamus (Jacobsen *et al.*, 2004). Nicotine nasal spray, however, had no effect on working memory (Myers *et al.*, 2004). While one study found a positive effect for nicotine nasal spray on verbal memory (Smith *et al.*, 2002), this effect was not seen for smoking (Sacco *et al.*, 2005; Smith *et al.*, 2002), nicotine gum (Harris *et al.*, 2004), or the nicotine patch (Levin *et al.*, 1996). Both nicotine nasal spray and the patch appear to improve complex reaction times (Levin *et al.*, 1996; Smith *et al.*, 2002), but there is no effect on simple reaction time (Levin *et al.*, 1996). Neither abstinence (George *et al.*, 2001) nor the reinitiation of smoking affects executive functioning (Sacco *et al.*, 2005). Finally, one study found an improvement in a visuospatial delayed recognition task following nicotine nasal spray in smokers (Myers *et al.*, 2004) while another study found no effect of nicotine gum on visuospatial abilities (Harris *et al.*, 2004).

Studies of the effect of nicotine on physiological abnormalities such as sensory gating and eye tracking have been more consistent. One of the first investigations of the effect of nicotine in persons with schizophrenia found that abnormal P50 auditory gating was normalized in persons with schizophrenia after smoking (Adler *et al.*, 1993). This finding was replicated using the nicotine patch (Griffith *et al.*, 1998). In a different paradigm of sensory gating, prepulse inhibition, smoking prior to testing results in better test performance than not smoking (Kumari *et al.*, 2001). Studies of smooth pursuit eye movements have been equally robust, with every study to date finding significant enhancement of performance using cigarette smoking (Olincy *et al.*, 1998, 2003), nicotine nasal spray (Avila *et al.*, 2003; Sherr *et al.*, 2002), and nicotine patch (Dépatie *et al.*, 2002). A functional magnetic resonance imaging study of the effects of nicotine on smooth pursuit eye movements found that nicotine enhanced cingulate and precuneus activation and decreased abnormally elevated hippocampal activation

(Tregellas *et al.*, 2004, 2005). Antisaccade task performance also improved following the administration of nicotine gum (Larrison-Faucher *et al.*, 2004).

While the physiological studies are all positive, the neurocognitive findings are less consistent. These studies are limited by the difficulties inherent in studies of any pharmacological agent, such as dosing and administrative route, as well as the specific difficulty present in administering nicotine in persons who are already dependent on the substance. One way to control for these difficulties is to use a population that is not dependent on nicotine such as nonsmokers with schizophrenia. While diminishing the generalizability of the results as well as making recruitment more difficult, this avoids the confounds of withdrawal and different long-term biological effects of smoking such as receptor upregulation and desensitization. Adler *et al.* (1992) took this approach one step further by first examining the effects of nicotine gum in the first-degree relatives of persons with schizophrenia who were impaired on the P50 auditory gating paradigm, thereby avoiding the additional confounds of the illness itself and the medications used to treat the illness. If one chooses to use schizophrenics who smoke, two types of difficulties arise. The first is how to deal with the issue of withdrawal. One must find a balance between clearing the system of the acute effects of nicotine while not precipitating symptoms of withdrawal that might affect performance. Our laboratory has advocated the use of a 2-h period of abstinence to balance these demands. The second issue is how to control for smoking status if using a comparison group of control smokers. While the test-retest reliability of the reported smoking history in persons with schizophrenia is quite high (0.92–0.99) and the intercorrelation of objective measures of smoking heaviness such as carbon monoxide, urine cotinine, and nicotine are fairly similar between persons with schizophrenia and controls (0.52–0.80), the relationship between the reported number of cigarettes smoked per day and these objective measures is much lower for persons with schizophrenia (0.02–0.37 vs 0.61–0.65; Yang *et al.*, 2003). Although not studied directly, this may be due to the greater extraction of nicotine in persons with schizophrenia (Olincy *et al.*, 1997). Despite these difficulties, however, there appears to be clear normalization of deficits in persons with schizophrenia following cigarette smoking or the administration of nicotine.

Nicotine, however, has several limitations as a therapeutic agent. Nicotine induces tachyphylaxis, as demonstrated by the inability of repeated dosing of nicotine to enhance impaired P50 auditory gating. Therefore, sustained benefit does not occur. While nicotine replacement eliminates many of the risks of the other ingredients and additives in tobacco, the long-term risks of chronic nicotine use are unknown and may include carcinogenic risk (Crowley-Weber *et al.*, 2003; Heusch and Maneckjee, 1998) and cerebro- or cardiovascular risk (Benowitz, 2003; Benowitz and Gourlay, 1997; Chalon *et al.*, 2000; Elliott *et al.*, 2003;

Fang *et al.*, 2003; Hakki *et al.*, 2002; West *et al.*, 2003). Furthermore, nicotine is an addictive agent, and the development of tolerance can lead to the stressful symptoms of withdrawal in the absence of continued nicotine dosing (Benowitz, 1998). Less potentially toxic and more chronically effective cholinergic treatments are needed.

An alternative to the use of nicotine as a nicotinic agonist would be to increase endogenous release of acetylcholine. For instance, clozapine is able to increase acetylcholine levels in hippocampus (Shirazi-Southall *et al.*, 2002). Consistent with this acetylcholine-enhancing effect, patients on clozapine have near normal levels of P50 suppression. The normalization of auditory gating over time parallels clinical improvement (Nagamoto *et al.*, 1999). Typical neuroleptics and the majority of atypical neuroleptics, however, have no effect on P50 auditory gating (Adler *et al.*, 2004; Freedman *et al.*, 1983; Yee *et al.*, 1998). Clozapine-induced normalization of auditory gating in DBA/2 mice is blocked by  $\alpha$ -bungarotoxin, implicating an  $\alpha$ 7 nicotinic receptor mechanism (Simosky *et al.*, 2003). Ondansetron, an antiemetic, also increases acetylcholine levels via 5HT-3 receptor antagonism. Similar to clozapine, it enhances P50 auditory gating in persons with schizophrenia (Adler *et al.*, 2005). The anticholinesterase inhibitor donepezil nonsignificantly enhanced the P50 auditory gating in persons with schizophrenia (Buchanan *et al.*, 2002). Although olanzapine is also able to increase acetylcholine levels in the hippocampus (Shirazi-Southall *et al.*, 2002), and a cross-sectional study has shown less impaired levels of auditory gating in people with schizophrenia treated with olanzapine (Light *et al.*, 2000), a more definitive cause and effect relationship has not been demonstrated with a longitudinal study (Arango *et al.*, 2003) and a second cross-sectional study found no differences between unmedicated schizophrenics and patients taking olanzapine (Adler *et al.*, 2004).

Interestingly, clozapine has also shown efficacy in its ability to reduce smoking levels in some (Combs and Advokat, 2000; George *et al.*, 1995; McEvoy *et al.*, 1999) but not every study of persons with schizophrenia (De Leon *et al.*, 2005). An additional study examining the effects of bupropion on smoking rates in persons with schizophrenia was confounded by clozapine use. The one abstinent person at 3 months and three of the four abstinent persons at a 2 year follow-up were also taking clozapine (Evins *et al.*, 2001, 2004). These findings may be consistent with a decreased need to self-medicate with cigarette smoking. However, this effect may not be unique to clozapine, as olanzapine and risperidone have also been shown to be associated with greater abstinence when compared to typical antipsychotics (George *et al.*, 2000). Despite its superior efficacy (Kane *et al.*, 1988) and these additional proposed benefits, treatment with clozapine is limited given the significant side effects of sedation, drooling, tachycardia, and weight gain as well as the serious potential side effects of seizures and agranulocytosis.

#### IV. The Search for an $\alpha 7$ Nicotinic Acetylcholine Receptor Agonist

Two compounds in current clinical use may have direct effects on  $\alpha 7$  nicotinic receptors. The anticholinesterase inhibitor galantamine, which has additional modulatory effects on the  $\alpha 7$  nicotinic receptor, has been reported to be beneficial for schizophrenia in a case study (Rosse and Deutsch, 2002). Tropisetron, a 5-HT<sub>3</sub> antagonist marketed outside the United States as an anti-nausea drug, also has efficacy as an  $\alpha 7$  nicotinic receptor agonist (Macor *et al.*, 2001; Papke *et al.*, 2005). Tropisetron increases the inhibition of P50 auditory gating in schizophrenia (Koike *et al.*, 2005), an effect due to actions at the  $\alpha 7$  nicotinic receptor (Hashimoto *et al.*, 2005).

In addition to these medications already being clinically utilized, several cholinergic receptor agonists have been developed to further characterize central nervous system cholinergic function and as potential candidates for the treatment of dementia of the Alzheimer's type (Kem, 2000). Drugs currently in development include a 1,4-diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-pyridin-2-yl-phenyl ester at Pfizer Inc., an (E)-*N*-methyl-5 (3-pyridinyl)-4-penten-2-amine at Targacept Inc., and a substituted-heteroaryl-7-aza[2.2.1]bicycloheptanes at Pharmacia & Upjohn Company. AR-R 17779, an Astra Arcus product, is an acetylcholine analogue with full agonist properties at the  $\alpha 7$  nicotinic receptor (Mullen *et al.*, 2000). ABT-418, while primarily functioning as an  $\alpha 4/\beta 2$  agonist, also has some agonist properties at the  $\alpha 7$  nicotinic receptor (Briggs *et al.*, 1995). Derivatives of the 5-HT<sub>3</sub> receptor antagonist tropisetron are currently in development (Macor *et al.*, 2001). 3-(2,4 Dimethoxy)benzylidene-anabaseine (DMXBA) is one of a series of compounds derived from anabaseine, an alkaloid found in marine worms (Kem *et al.*, 1971, 1997; Meyer *et al.*, 1998c). DMXBA is a partial agonist at the  $\alpha 7$  receptor (Briggs *et al.*, 1995; De Fiebre *et al.*, 1995) and is a weak competitive antagonist at  $\alpha 4/\beta 2$  nicotinic (Kem *et al.*, 1996; Meyer *et al.*, 1998a; Papke *et al.*, 2000) and 5HT-3 receptors. Although the metabolites of DMXBA are also active at these receptors, their biological effect may be limited by their greater polarity and consequently, greater difficulty in crossing the blood-brain barrier (Kem *et al.*, 2004).

The efficacy of  $\alpha 7$  nicotinic receptor agonists has also been assessed in multiple animal paradigms of learning and memory (Levin and Rezvani, 2000; Levin and Simon, 1998). DMXBA improves memory-related behaviors in multiple paradigms, including a delayed matching to sample task (Briggs *et al.*, 1997), nonspatial avoidance task (Arendash *et al.*, 1995; Meyer *et al.*, 1994, 1997, 1998b), a 17-arm maze (Arendash *et al.*, 1995), and the Morris water maze (Meyer *et al.*, 1997). DMXBA also improves learning behavior as evidenced by enhanced performance during eye blink classical conditioning acquisition (Woodruff-Pak, 2003; Woodruff-Pak *et al.*, 1994) and performance in the Lashley III maze

(Arendash *et al.*, 1995). Some of these beneficial effects may be mediated by enhancement of long-term potentiation in hippocampal cells, a process important in learning and memory formation (Hunter *et al.*, 1994). Finally, a mouse model of schizophrenia-like cognitive and deficit symptoms, “popping,” induced by the administration of a *N*-methyl-D-aspartic acid receptor antagonist is reduced following the administration of anabaseine (Mastropaolo *et al.*, 2004).

Given the known role of  $\alpha 7$  nicotinic receptors in auditory gating, these drug candidates have also been tested for their ability to reverse auditory gating in animal models. As hypothesized, subcutaneous administration of DMXBA normalizes auditory gating in DBA/2 mice (Stevens *et al.*, 1998). Furthermore, a second injection of DMXBA produces a similar enhancement of inhibition. This lack of tachyphylaxis may represent improved efficacy of DMXBA in normalizing auditory gating on a chronic basis (Stevens *et al.*, 1998, 1999). Intragastrically administered DMXBA also enhanced impaired auditory gating, demonstrating that the medication can be effectively administered on an oral basis and is still efficacious at normalizing impaired auditory gating (Simosky *et al.*, 2001). DMXBA failed in another more complex and strain-dependent model of sensory gating, prepulse inhibition (Olivier *et al.*, 2001; Schreiber *et al.*, 2002). Despite this lack of effect of  $\alpha 7$  nicotinic receptor agonists on prepulse inhibition measures, the robust reversal of P50 auditory gating deficits in these animal models is very promising for a similar effect in studies of auditory gating and cognition in schizophrenia.

#### V. The Phase 1 Study of DMXBA in Schizophrenia

On the basis of the success of preclinical trials of  $\alpha 7$  agonists in animal models of learning and memory and the safety of these drugs, DMXBA was initially evaluated in normal subjects with a planned development for the treatment of dementia of the Alzheimer’s type. DMXBA was found to significantly improve simple reaction time, correct detection during digit vigilance, both word and picture recognition memory, and both immediate and delayed word recall. Additionally, DMXBA improved subject performance speed on a numeric and spatial working memory task. Improvement was seen at doses from 25 to 150 mg with minimal adverse events (Kitagawa *et al.*, 2003). Despite these promising results, further development of DMXBA was not pursued by Taiho Pharmaceuticals. However, following the correction of the P50 auditory gating deficit by nicotine in persons with schizophrenia, the evidence of the  $\alpha 7$  nicotinic receptor’s role in this gating deficit in animal studies, as well as the reversal of sensory gating abnormalities in an animal model by the  $\alpha 7$  nicotinic receptor agonist DMXBA,

this drug was identified as a potential candidate in the treatment of cognitive dysfunction in schizophrenia (Martin *et al.*, 2004).

A second phase I trial of DMXBA has been conducted in persons with schizophrenia (Olincy *et al.*, 2006). During this 3-visit study, DMXBA was administered in a double-blind fashion to 12 persons with schizophrenia. Doses were either placebo, a 75-mg dose with a 37.5-mg follow-up dose, or a 150-mg dose with a 75-mg follow-up dose. Subjects then underwent P50 auditory gating as well as neurocognitive testing. DMXBA normalized the P50 ratio (effect size of 2.36) as well as the test wave amplitude (effect size 1.45), a more specific measure of inhibition (Fig. 1). These findings are an improvement over the study of nicotine on P50 auditory gating in relatives (effect size 0.86). DMXBA was also

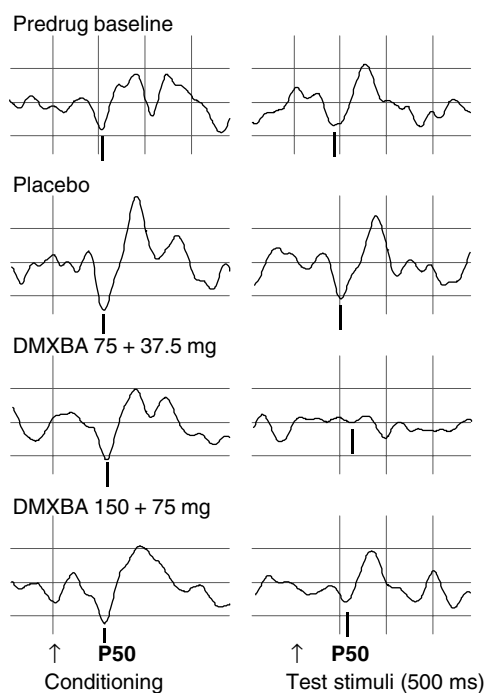


FIG. 1. Auditory-evoked responses of a subject with schizophrenia. Stimuli were a conditioning auditory stimulus and an identical test stimulus, delivered 500 ms apart. Inhibition of the test P50 response is increased by DMXBA administration, particularly during the lower dose (third row), compared to baseline and placebo responses above it. Arrows show the timing of the stimuli and vertical bars mark the location of the P50 wave in the tracings above. Positive polarity is downwards; vertical grid interval is  $2 \mu\text{V}$ , and horizontal is 50 ms. This figure is reproduced with permission from Olincy *et al.* (2006). Proof-of-concept trial of an  $\alpha 7$  nicotinic agonist in schizophrenia. *Arch. Gen. Psychiatry*, June 2006, **63**, 630–638; Copyright © 2006, American Medical Association. All rights reserved.

able to improve performance on both the Repeatable Battery for the Assessment of Neuropsychological Status' (RBANS) Total Scale score (effect size 1.8) as well as the Attention subscale (effect size 2.17; Fig. 2). These effect sizes are much larger than those seen for nicotine on the RBANS (0.6 and 0.25 for the Total scale score and Attention subscale score, respectively; Harris *et al.*, 2004) as well as for multiple other tests of the actions of nicotine on cognition in schizophrenia (effect sizes of 0.27–1.3; Dépatie *et al.*, 2002; Levin *et al.*, 1996; Myers *et al.*, 2004; Sacco *et al.*, 2005; Smith *et al.*, 2002). Furthermore, the effect sizes seen with DMXB A were also favorable when compared to the typical effect sizes of 0.2–0.5 for the effect of second generation antipsychotics on attentional and composite cognitive scores in persons with schizophrenia (Keefe *et al.*, 2004). The positive effects of DMXB A on sensory gating and cognition were not related to any changes in Brief Psychiatric Rating Scale scores and were therefore not due to changes in positive, negative, or anxiety-related symptoms.

These findings provide further evidence for a role of the nicotinic cholinergic system in the pathology of schizophrenia. Furthermore, specific  $\alpha 7$  nicotinic cholinergic agonism is a therapeutic mechanism that provides hope for the

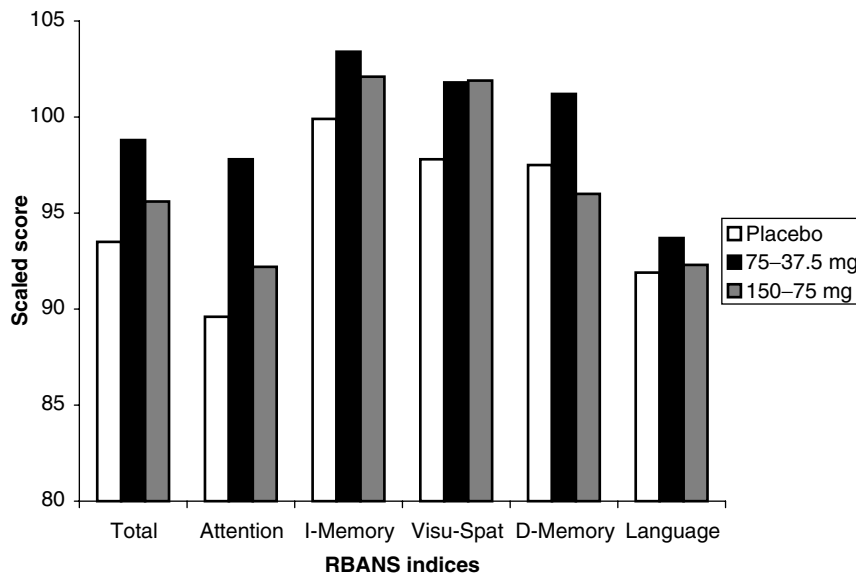


FIG. 2. Effects of DMXB A and placebo on the RBANS Total Scale score and its specific indices. I is immediate and D is delayed memory. This figure is reproduced with permission from Olincy *et al.* (2006). Proof-of-concept trial of an  $\alpha 7$  nicotinic agonist in schizophrenia. *Arch. Gen. Psychiatry*, June 2006, **63**, 630–638; Copyright © 2006, American Medical Association. All rights reserved.

treatment of cognitive deficits in schizophrenia. As cognitive symptoms are more closely related to psychosocial dysfunction than traditional positive symptoms, such as hallucinations and delusions (Green, 1996), such a treatment could substantially increase the quality of life for persons with this devastating illness and reduce the financial burden of this disease.

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