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Treating schizophrenia symptoms with an α7 nicotinic agonist, from mice to men

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ABSTRACT

Current antipsychotic treatments fail to fully address the range of symptoms of schizophrenia, particularly with respect to social and occupational dysfunctions. Recent work has highlighted the role of nicotinie in both cognitive and attentional deficits as well as deficient processing of repetitive sensory information. The predilection for schizophrenia patients to be extremely heavy cigarette smokers may be related to their attempt to compensate for a reduction in hippocampal α7 nicotinic cholinergic receptors by delivering exogenous ligand to the remaining receptors. Studies in rodent models of both learning and memory deficits and deficits in sensory inhibition have confirmed a role for the α7 subtype of the nicotinic cholinergic receptor in these processes. Rodent studies also demonstrated the efficacy of a selective partial α7 nicotinic agonist, DMXBA, to improve these deficits. Subsequent human clinical trials demonstrated improved sensory inhibition in 12 schizophrenia patients and showed improvement in several subtests of the RBANS learning and memory assessment instrument. These data suggest that therapeutic agents selected for α7 nicotinic activity may have utility in treating certain symptoms of schizophrenia.

Although the positive symptoms such as hallucinations and delusions of schizophrenia are partially treated with the available antipsychotic medications, social and occupational dysfunction remains a major issue in treating this disorder. Cognitive deficits have been identified as more closely related to ability to adequately function [1]. In the search for new and more effective therapeutic agents for schizophrenia, recent attention has turned the nicotinic cholinergic receptor system.

1. α7 and P50 auditory gating

People with schizophrenia, in addition to the cardinal symptoms of hallucinations and delusions, suffer from the inability to focus attention. This may stem from being overwhelmed by extraneous sensory stimuli [2] which impairs the person's ability to think coherently. 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 [3]. The P50 auditory evoked response occurs 40–75 ms after the presentation of a brief click. This 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 non-essential noise. This results in a diminished amplitude of the P50 component of the evoked response to the second stimulus relative to the first (Fig. 1). Persons with schizophrenia generally show less ability to inhibit or filter out

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Abbreviations: DMXBA, 3-[2,4-dimethoxybenzylidene]anabaseine; PPI, prepulse startle inhibition; RBANS, repeatable battery for assessment for neuropsychological status; SNP, single nucleotide polymorphism

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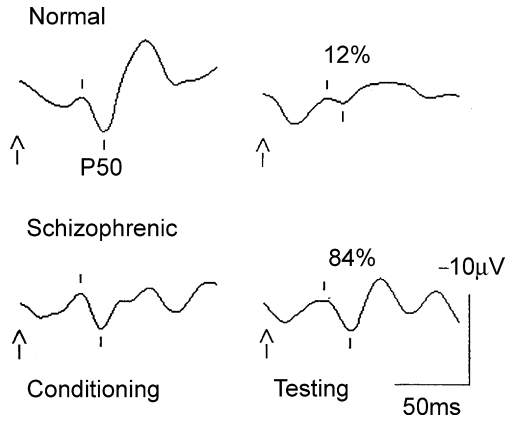

Fig. 1 – P50 auditory evoked potentials from a control and schizophrenia patient. The arrows indicate the onset of the stimuli. The tick marks delineate the peak and trough of the P50 evoked response wave. In the normal subject, the test amplitude is 12% of the conditioning amplitude demonstrating the suppression of response to the second of paired identical tones. The schizophrenic patient shows a test amplitude of 84% of the response of the conditioning amplitude. (Adapted from Adler et al. 1990).

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 [4–7] This deficit is correlated with impairment in sustained attention as measured by diminished performance on the digit vigilance test [8].

People with schizophrenia frequently smoke cigarettes and often smoke heavier than the normal population [9–15]. Additionally, they extract more nicotine from each cigarette they smoke, presumably by deeper inhalation [16]. The high level of smoking has been proposed as a form of self-medication to alleviate symptoms of their illness including depression, anxiety, anhedonia or amotivation [16–19]. Others have proposed that smoking alleviates symptoms of nicotine withdrawal or neuroleptic-induced side effects [20–23,11]. Finally, smoking may be an attempt to improve cognition and sensory gating [24–26].

Nicotine appears to have a positive effect on P50 inhibition in schizophrenia [26]. 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. Longer lasting effects are not seen with the transdermal patch, demonstrating that prolonged effects cannot be obtained with this method of administration because of tachyphylaxis [27]. Relatives of people with schizophrenia also have poor P50 suppression without the confounds of the additional pathological effects of schizophrenia, the effects of medications or chronic smoking [28–31]. People with schizophrenia treated with clozapine exhibit normalization of their P50 ratio coincident with improvement in their clinical symptoms [32]. Clozapine, which releases acetylcholine in the hippocampus [33], may thereby indirectly act on the nicotinic cholinergic receptors to normalize the P50 ratio, as people with schizophrenia also decrease the amount of cigarettes they smoke while taking this medication [34,35]. Clozapine also has the property of 5HT3 antagonism, which indirectly activates nicotinic cholinergic receptors. Nicotine gum and physostigmine also improve P50 suppression in relatives of people with schizophrenia [36]. Administration of high dose nicotine with 10 mg of mecamylamine, a high affinity $\alpha4\beta2$ nicotinic cholinergic receptor antagonist still produces improvement in P50 suppression in schizophrenia [37] (Fig. 2). Thus, since nicotine is a non-selective agonist and mecamylamine is blocking the high affinity receptors, the improvement in suppression appears to be mediated through the low affinity $\alpha7$ nicotinic cholinergic receptors.

Additional independent evidence for involvement of the $\alpha7$ cholinergic receptor in the P50 auditory evoked potential

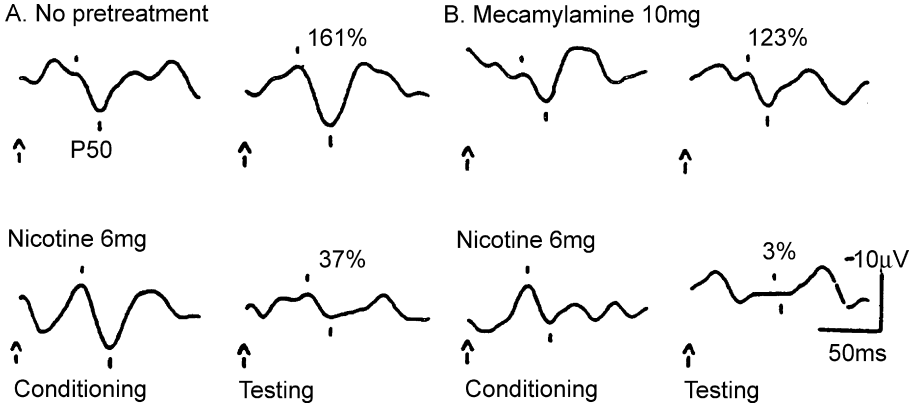

Fig. 2 – (A) The P50 auditory gating deficit in the relative of a schizophrenic patient (left upper panel) with a lack of inhibition. The arrows indicate the onset of the stimuli. The tick marks delineate the peak and trough of the P50 evoked response wave. The test amplitude is initially 161% of the conditioning amplitude. After nicotine gum, the P50 evoked response is normalized as indicated by a test amplitude of 37% of the conditioning amplitude (left lower panel); (B) with pretreatment with mecamylamine (right upper panel) blockade of the $\alpha2\beta4$ high affinity receptor does not block the effect of nicotine (right lower panel) thus the test amplitude is 3% of the conditioning amplitude. The enhancement of the effect may be caused by mecamylamine's blockade of the stimulatory effect of nicotine on catecholamine release, which is mediated through high affinity nicotinic receptors (Adapted from Freedman et al. 1994).

deficit is provided through genetics. Nine multiplex families with schizophrenia were studied in a genome-wide linkage analysis. 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, $\Theta = 0.0$ [38]. Linkage of this region to schizophrenia was further replicated in families from the NIMH schizophrenia genetics initiative [39] and in other studies [40–43], but there have also been some negative studies in this region [44,45]. 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 [46,47]. Furthermore, the presence of a SNP in the 15q14 gene CHRNA7 5′ core promoter is significantly associated with P50 suppression deficits [46]. 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 [46,47].

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 cholinergic receptors. Decreased α7 nicotinic cholinergic receptor binding has been noted in the reticular nucleus of the thalamus, the hippocampus, the cingulate cortex and the frontal lobe regions [48–51].

A similar deficit in sensory gating has been found in inbred mice. The DBA/2 strain exhibits a failure to suppress its response to the second stimulus in a paradigm identical to that used with humans, while the C3H shows a pattern comparable to normal humans [52] (Fig. 3). Studies have shown that the sensory gating improves in the DBA/2 mouse with nicotine administration [53], just as it does in schizophrenia patients [26]. Additionally, similar effects were found for clozapine in both the DBA/2 mouse [54] and schizophrenia patients [32]. The mechanism of sensory gating has been clarified through the use of these animal models. The activation of the α7 cholinergic receptors releases GABA from GABAergic interneurons [55,56] 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 [57]. Nitric oxide acts as a second messenger to prolong the effect of the α7 nicotinic cholinergic receptor stimulation. Additionally, a promoter region polymorphism exists between the CH3 and the DBA/2 mouse strains [58] which models the polymorphisms observed in the human promoter region [38]. Thus, the DBA/2 mouse represents a useful model of the sensory gating deficit in schizophrenia from both the phenotypic and genotypic standpoint. The DBA/2 mouse also shows a reduction in the number of hippocampal α7 nicotinic cholinergic receptors [52] similar to what is observed in humans with schizophrenia [49].

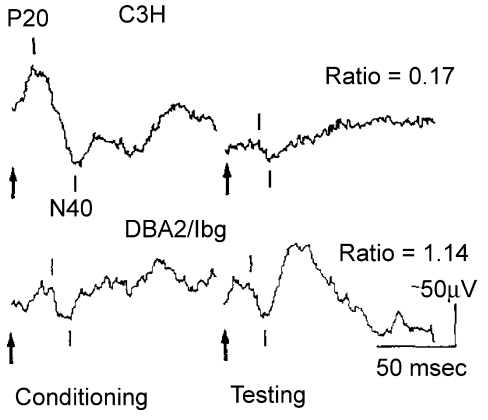

Fig. 3 – Auditory evoked potentials in response to identical paired stimuli in two inbred strains of mouse. The arrows indicate the onset of the stimuli. The tick marks delineate the peak and trough of the N40 evoked response wave. The C3H strain models the pattern seen with human control subjects with a test amplitude that is 17% of the conditioning amplitude, demonstrating inhibition of the evoked potential. The DBA/2 mouse shows a pattern similar to that observed in schizophrenia patients, with a test amplitude of 114% of the conditioning amplitude, and a lack of inhibition of the evoked response. (Adapted from Stevens et al. 1996).

2. α7 in learning and memory

Although nicotine seems to improve cognition, the involvement of high or low affinity nicotinic cholinergic receptors is unclear. Withdrawal from nicotine in normal smokers has been shown to cause attention impairments [59]. 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 with decreased errors of omission without an increase in errors of commission [60]. In Alzheimer's disease, where nicotinic cholinergic receptors are known to be decreased in the cortex and hippocampus [61,62], nicotine injections or nicotine skin patches significantly improve attention, learning and memory [63–68]. Similarly, in adults with attention deficit disorder, the nicotine skin patch reduces clinical symptoms and increases reaction time, but does not improve errors of omission in the continuous performance test [69].

The effects of nicotine on neuropsychological measures in persons with schizophrenia, unlike the effects on the P50 auditory evoked potential are less conclusive. In smokers with schizophrenia, with abstinence from nicotine, working memory is decreased [70,71]. If nicotine is then reinitiated by smoking, working memory deficits are normalized [71]. There have been several studies using the nicotine patch to administer nicotine. One study induced memory deficits with haloperidol. The nicotine patch was then applied and was able to restore functioning to baseline as measured before the administration of haloperidol [72]. In another study, the nicotine patch also improved auditory working memory, attention, and complex reaction times but not simple reaction times [72–74]. Nicotine gum shows mixed effects depending on the psychological realm and whether the subjects are smokers or are non-smokers. While nicotine gum improves attention in non-smokers, it may diminish attention in smokers. In contrast, nicotine gum has no effect in either smokers or non-smokers on working memory or visuospatial memory [75].

Finally, nicotine nasal spray enhances verbal memory [76], visuospatial delayed recognition [77] and complex reaction times but has no effect on simple reaction times attention or working memory [72,78,77]. 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.

3. DMXBA as a prototype drug

Nicotine has several limitations as a therapeutic agent for schizophrenia. Nicotine induces tachyphylaxis and thus does not maintain sustained benefit. 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 [79]. Thus, alternative nicotinic agonists that are less potentially toxic would be helpful in the treatment of schizophrenia.

One of the few agents that has reached clinical trials is GTS-21 or 3-[2,4-dimethoxybenzylidene]anabaseine (DMXBA). This is one of a series of compounds derived from anabaseine, an alkaloid found in marine worms [80,81]. DMXBA is a partial agonist at the α7 nicotinic cholinergic receptor [82,83] and a weak competitive antagonist at α4β2 nicotinic cholinergic receptors and $5HT_3$ receptors [84,85]. The first step in testing of this compound was to administer DMXBA to DBA/2 mice. This compound produced a dose-dependent improvement in sensory gating in this model (Fig. 4A) which occurred through a selective reduction in the response to the second stimulus (Fig. 4B) [86]. This pattern is in concert with what is now known regarding nicotinic modulation of the two evoked potentials, that is that modulation of the response to the second stimulus is mediated by α7 nicotinic cholinergic receptors [87] while the response to the first stimulus is mediated, in part, by α4β2 nicotinic cholinergic receptors [88]. Thus, increased stimulation of the limited numbers of hippocampal α7 nicotinic cholinergic receptors with DMXBA in this mouse strain increases firing of the interneurons, on which they reside [89], which in turn inhibits firing of a subpopulation of pyramidal cells in response to the second stimulus. Antagonism of the α4β2 receptors blocks any stimulation by endogenous acetylcholine, thus inhibiting increases in the response to the first stimulus, as is

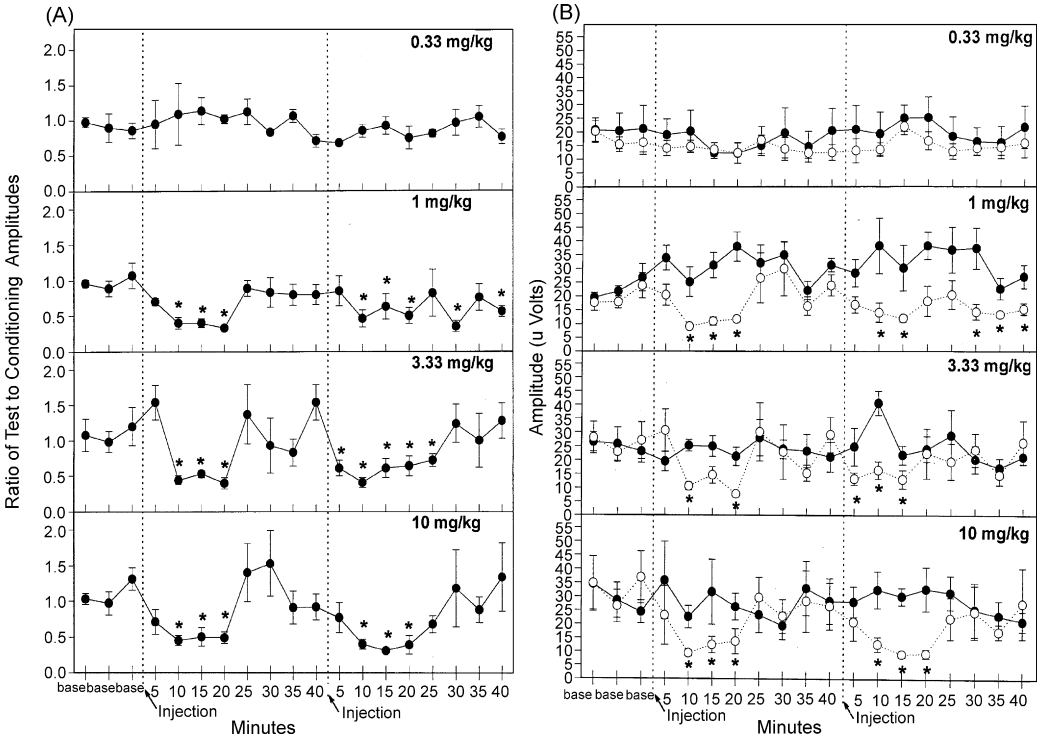

Fig. 4 – (A) The effect of DMXBA on the ratio of the amplitude of the second auditory evoked response divided by the amplitude of the response to the first stimulus. DMXBA dose dependently lowered the ratio showing improvement in sensory gating in the DBA/2 mouse, a model of schizophrenia-like deficits in sensory gating. DMXBA was administered as indicated by the arrows labeled injection. Asterisks indicate ratios that are significantly different from predrug baseline. Filled circles indicate mean N40 ratio. (B) DMXBA was administered as indicated by the arrows labeled injection. The improvement in auditory gating with this compound was produced by a selective decrease in the response to the second stimulus demonstrating increased inhibition in the circuitry. The records were obtained in the CA3 region of the hippocampus in response to paired identical auditory stimuli. The DMXBA was administered subcutaneously and recordings obtained at 5 min intervals. At 40 min, when the responses were back to baseline levels, a second identical injection was administered and recordings were obtained for an additional 40 min. Filled circles indicate mean conditioning amplitude. Open circles indicate mean test amplitude. Asterisks indicate amplitudes that are significantly different from baseline (Adapted from Stevens et al. 1998).

commonly observed with non-selective agonists such as nicotine [53]. The improvement in sensory gating has been replicated in isolation-reared rats which show deficient sensory gating [90], in C3H mice chronically treated with cocaine, which also show deficient sensory gating [91] and after oral administration of DMXBA in DBA/2 mice [92].

An alternate method for assessing deficiencies in sensory processing is the prepulse startle inhibition (PPI) paradigm in which a small auditory stimulus preceding a large startling auditory stimulus reduces the amplitude of the startle response induced by the large stimulus [93]. Schizophrenia patients do not show normal PPI [94], but smoking improves the deficit [95,96]. In rodent studies, nicotine improves PPI in a model of deficient schizophrenia-like PPI [97]. Administration of DMXBA also improves deficient PPI [98].

Finally, cognitive and attentional deficits are a recognized symptom class in schizophrenia [99–101] which can be improved with nicotine administration [102,74–76]. Various paradigms have been developed to assess similar learning and memory, and attention functions in rodents, and similar to what is seen in humans, nicotine has been shown to improve rodent deficits in these paradigms [103–107]. DMXBA improves monkey performance on a delayed matching to sample task, an effect that persists for 24 h after drug administration [108]. The administration of DMXBA improves eyeblink classical conditioning acquisition in older rabbits who have lost cholinergic neurons [109]. Mecamylamine, an $\alpha4\beta2$ antagonist has a deleterious effect on conditioned learning in young rabbits. If young rabbits are given mecamylamine and DMXBA, their eyeblink classical conditioning acquisition is improved [110]. DMXBA improves one-way active avoidance, Lashley III maze testing, and 17 arm radial maze test performance in aged rats [111,112]. Passive avoidance deficits are normalized in rats [113], and ischemia-induced hippocampal cell death and impaired passive avoidance performance in gerbils are prevented by treatment with DMXBA [114]. DMXBA also improves performance on the Morris water maze [115].

The first stage in human testing with DMXBA was to initially administer this compound to normal male subjects to assess for safety, tolerability, pharmacokinetics and possible effects on cognition prior to its study as a cognitive enhancer in Alzheimer's disease [116]. Subjects were randomized to DMXBA (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 reaction time, choice reaction time, 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. DMXBA was well tolerated at doses of up to 450 mg daily with no significant safety findings. DMXBA significantly improved performance on simple reaction time, choice 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 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 [116].

As this agent appeared safe and promising in enhancing cognition, DMXBA was studied in schizophrenia to prove that the $\alpha7$ nicotinic cholinergic receptor activation is responsible for the normalization of the P50 auditory evoked potential deficit in schizophrenia. Additionally, the safety and effects of this agent on neurocognition in this population were also evaluated [117]. DMXBA was administered in a double-blind, placebo-controlled cross-over design to 12 male and female non-smokers with schizophrenia. All subjects had been stable on their normal antipsychotic medications for at least 3 months. DMXBA was administered orally (150 or 75 mg) followed 2 h later by a half dose (75 or 37.5 mg). The half dose, administered at the predicted half-life of the first dose was chosen to extend the period of therapeutic drug levels during the behavioral measurements. Subjects received the high and low doses and identical appearing placebos, randomly on three different days. Study days were at least 3 days apart. The repeatable battery for assessment for neuropsychological status (RBANS), which assesses attention, immediate memory, visuo-spatial/construction, language and delayed memory [118], was administered immediately following the second dose on each experimental day. The P50 auditory evoked potential and brief psychiatric rating scales were recorded at baseline before drug administration, twice after the first and once after the second dose. DMXBA improved performance on both the RBANS total scale score (effects size 1.8) as well as the attention subscale (effect size 2.17; Fig. 5; [117]). These effect sizes are much larger that those seen for nicotine on the RBANS (0.6 and 0.25 for the Total scale score and Attention subscale score, respectively [75]. DMXBA also 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. These findings are an improvement over the study of nicotine on P50 auditory gating in relatives (effect size of 0.86; Fig. 6; [117]). Increased inhibition of the P50 response during DMXBA is consistent with the hypothesized agonist effect on $\alpha7$ receptors. DMXBA seems to be beneficial at low concentrations and less effective at higher concentrations. This suggests that there may be tachyphylaxis, but a larger number of subjects is required to establish this point. At this stage of the investigation, the difference between the two doses is not significant. In animal studies with DMXBA, there was no tachyphylaxis to repeated dosing, but a non-significant indication of decreased effect was observed at higher doses.

4. Other potential nicotinic targets

A series of other putative cholinergic receptor agonists have been developed as potential candidates for the treatment of schizophrenia and Alzheimer's disease. Drugs currently in development include a 1,4-diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 4-pyridin-2yl-phenyl ester at Pfizer Inc., and a N-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide (14 PHA-543,613) also at Pfizer, Inc. 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 [119].

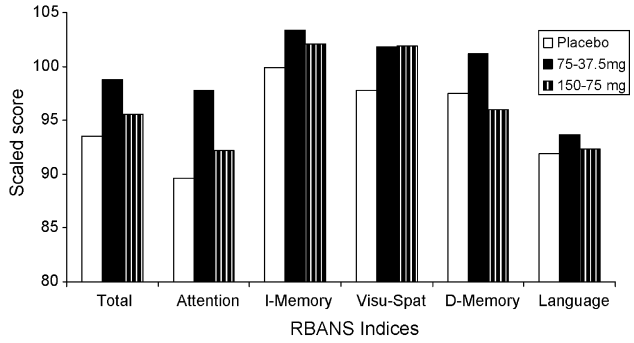

Fig. 5 – Effects of DMXB-A and placebo on the RBANS Total Scale Score and its specific Indices. I is immediate and D is delayed Memory Visu-Spat = visuospatial memory. (Adapted from Olincy et al. 2006).

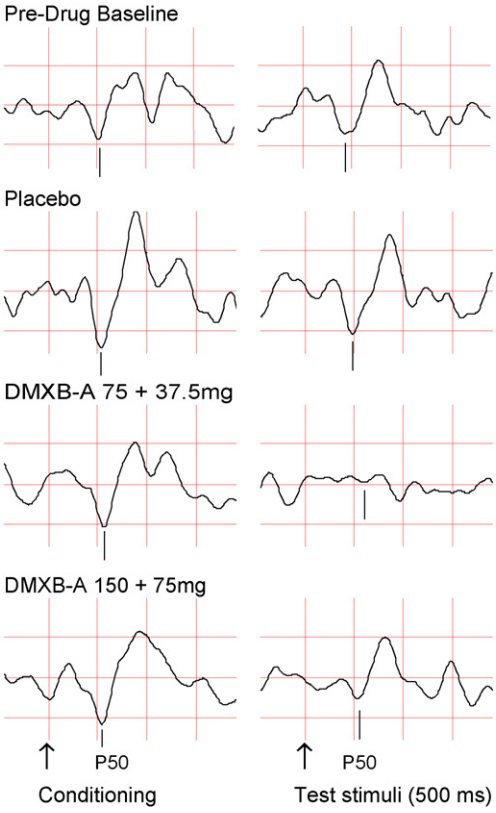

Fig. 6 – Auditory evoked responses of a subject with schizophrenia. Stimuli were a conditioning auditory stimulus and an identical test stimulus, delivered 500 ms apart. Inhibition of the test P50 response is increased by DMXB-A administration, particularly during the lower dose (third row), compared 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 μV, and horizontal is 50 ms. (Adapted from Olincy et al. 2006).

Targacept, Inc. has an (E)-*N*-methyl-5 (3-pyridinyl)-4-penten-2-amine and Pharmacia & Upjohn Company has a substituted-heteraryl-7-aza[2.2.1]bicycloheptane. SSR180711, a selective α7 nicotinic cholinergic receptor partial agonist from Sanofi-Adventis, enhances episodic memory in the object recognition task in rats preadministered methyllycaconitine, an α7 nicotinic cholinergic receptor antagonist, and in mice. However, when administered to α7 knockout mice, there is no enhancement of long-term episodic memory [120]. AR-R 17779, an AstraZeneca product, is an acetylcholine analogue with full agonist properties at the α7 nicotinic cholinergic receptor. This compound does not enhance the inhibition of startle in DBA/2 mice [121–123] or improve accuracy and speed of response on a five-choice serial reaction time [124,125]. ABT-418, has some agonist properties at the α7 nicotinic cholinergic receptors, but is a less potent agonist than nicotine [83] and restores deficient auditory gating in DBA/2 mice as well as rats with fimbria-fornix lesions, but similar to nicotine, fails to produce continued improvement with a second dose [53].

Two compounds that have been assessed in humans have used alternatives strategies to the use of nicotinic agonists to increase the endogenous release of acetylcholine. Ondansetron, an antiemetic, increases acetylcholine levels via $5HT_3$ receptors antagonism. Ondansetron enhances P50 auditory suppression in persons with schizophrenia 2 h after acute dosing [126]. Tropisetron, also a $5HT_3$ antagonist marketed outside the United States as an antinausea drug, also has efficacy as an α7 nicotinic cholinergic receptor agonist [127,128]. Low dose tropisetron increased the inhibition of the P50 auditory evoked potential differentially in non-smokers with schizophrenia [129], with no effect seen on smokers with schizophrenia. Consistent with a previous finding of the effect in smokers [75] the authors proposed that the nicotinic cholinergic receptors were chronically densensitized and that additional nicotinic agonism was blocked in smokers.

5. Discussion

The α7 nicotinic cholinergic receptor role in schizophrenia has been established through multiple independent pathways. An initial clinical observation of increased frequency of smoking in schizophrenia lead to the observation that these patients extract more nicotine from the cigarettes they smoke than do other smokers [15,10]. Examination of the symptom of being overwhelmed by extraneous sensory stimuli lead to finding a physiological deficit, the P50 auditory evoked potential, which corrects with the administration of nicotine in both an animal model and in humans [53,26]. This P50 auditory evoked potential deficit is linked to 15q14 at a polymorphic marker <120 kb from the α7 gene [38]. Postmortem studies which demonstrate decreased α7 nicotinic cholinergic receptor binding have been noted in the reticular nucleus of the thalamus, the hippocampus, the cingulate cortex and the frontal lobe regions [48–51]. Nicotine has brief cognitive-enhancing effects in schizophrenia [72–78]. However, nicotine has several limitations as a therapeutic agent for schizophrenia. Nicotine induces tachyphylaxis and thus does not maintain sustained benefit. Additionally, the long-term health risks of chronic nicotine use are unknown and nicotine is also addictive [79]. Thus, alternative nicotinic agonists that are less

potentially toxic would be helpful in the treatment of schizophrenia. The first agent which has proved successful in early testing for enhancement of cognition is DMXBA, a partial agonist at the α7 nicotinic cholinergic receptor [82,83] and a weak competitive antagonist at the α4β2 nicotinic cholinergic receptor and $5HT_3$ receptors [84,85,117]. Additionally, P50 auditory gating was also improved with DMXBA treatment [117]. DMXBA 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 non-smokers to avoid interactions of nicotinic agonists with already desensitized nicotinic cholinergic receptors, a trial of these types of drugs in smokers is warranted. Furthermore, the half-life of DMXBA is relatively short with a peak effect at about 2 h, requiring frequent administration which makes 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.

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REFERENCES

[1] Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schiophrenia: are we measuring the "right stuff"? Schizophr Bull 2000;26:119–36.
[2] Venables PH. Hippocampal function and schizophrenia: experimental psychological evidence. Ann NY Acad Sci 1992;658:111–27.
[3] Adler LE, Waldo MC, Freedman R. Neurophysiologic studies of sensory gating in schizophrenia: comparison of auditory and visual responses. Biol Psychiatry 1985;20:1284–96.
[4] Boutros NN, Zouridakis G, Overall J. Replication and extension of P50 findings in schizophrenia. Clin Electroencephalogr 1991;22:40–5.
[5] Judd L, McAdams L, Budnick B, Braff DL. Sensory gating deficits in schizophrenia: new results. Am J Psychiatry 1992;149:488–93.
[6] Ward PB, Hoffer LD, Liebert B, Catts SV, O'Donnell M, Adler LE. Replication of a P50 auditory sensory gating deficit in Australian patients with schizophrenia. Psychiatry Res 1996;64:121–35.
[7] Clementz BA, Geyer MA, Braff DL. P50 suppression among schizophrenia and normal comparison subjects: a methodological analysis. Biol Psychiatry 1997;41:1035–44.
[8] Cullum CM, Harris JG, Waldo MC, Smernoff E, Madison A, Nagamoto HT, et al. Neurophysiological and neuropsychological evidence for attentional dysfunction in schizophrenia. Schizophrenia Res 1993;10:131–41.
[9] Masterson E, O'Shea B. Smoking and malignancy in schizophrenia. Br J Psychiatry 1984;145:429–32.
[10] Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA. Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 1986;143:993–7.
[11] Goff DC, Henderson DC, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. Am J Psychiatry 1992;149:1189–94.
[12] Diwan A, Castine M, Pomerleau CS, Meador-Woodruff JH, Dalack GW. Differential prevalence of cigarette smoking in patients with schizophrenia vs. mood disorders. Schizophrenia Res 1998;33:113–8.
[13] Kelly C, McCreadie RG. Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. Am J Psychiatry 1999;156:1751–7.
[14] Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA 2000;284:2606–10.
[15] De Leon J, Dadvand M, Canuso C, Odom White A, Stanilla JK, Simpson GM. Schizophrenia and smoking: an epidemiological survey in a state hospital. Am J Psychiatry 1995;152:453–5.
[16] Olincy A, Young DA, Freedman R. Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. Biol Psychiatry 1997;42:1–5.
[17] Glassman AH. Cigarette smoking: implications for psychiatric illness. Am J Psychiatry 1993;150:546–53.
[18] Svensson TH, Grenhoff J, Engberg G. Effect of nicotine on dynamic function of brain catecholamine neurons. Ciba Foundation Symp 1990;152:169–80.
[19] Tung CS, Grenhoff J, Svensson TH. Nicotine counteracts midbrain dopamine cell dysfunction induced by prefrontal cortex inactivation. Acta Physiol Scand 1990;138:427–8.
[20] Nisell M, Nomikos GG, Svensson TH. Nicotine dependence, midbrain dopamine systems and psychiatric disorders. Pharmacol Toxicol 1995;76:157–62.
[21] Dalack GW, Meador-Woodruff JH. Smoking, smoking withdrawal and schizophrenia: case reports and a review of the literature. Schizophrenia Res 1996;22:133–41.
[22] Dalack GW, Becks L, Hill E, Pomerleau OF, Meador-Woodruff JH. Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. Neuropsychopharmacology 1999;21:195–202.
[23] Decina P, Caracci G, Sandik R, Berman W, Mukherjee S, Scapicchio P. Cigarette smoking and neuroleptic-induced parkinsonism. Biol Psychiatry 1990;28:502–8.
[24] Taiminen TJ, Salokangas RKR, Saarijärvi S, Niemi H, Lehto H, Ahola V, et al. Smoking and cognitive deficits in schizophrenia: a pilot study. Addict Behav 1998;23:263–6.
[25] Nomikos GG, Schilström B, Hildebrand BE, Panagis G, Grenhoff J, Svensson TH. Role of alpha-7 nicotinic receptors in nicotine dependence and implications for psychiatric illness. Behav Brain Res 2000;113:97–103.
[26] Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 1993;150:1856–61.
[27] Griffith JM, O'Neill J, Petty F, Garver D, Young D, Freedman R. Nicotinic receptor desensitization and sensory gating deficits in schizophrenia. Biol Psychiatry 1998;44:98–106.
[28] Siegal C, Waldo MC, Mizner G, Adler LE, Freedman R. Deficits in sensory gating in schizophrenic patients and their relatives. Arch Gen Psychiatry 1984;41:607–12.
[29] Waldo MC, Carey G, Myles-Worsley M, Cawthra E, Adler LE, Nagamoto HT, et al. Codistribution of a sensory gating deficit and schizophrenia in multi-affected families. Psychiatry Res 1991;39:257–68.
[30] Clementz BA, Geyer MA, Braff DL. Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. Am J Psychiatry 1998;155:1691–4.
[31] Ross RG, Olincy A, Harris JG, Radant A, Hawkins M, Adler LE, et al. Evidence for bilineal inheritance of physiological

indicators of risk in childhood-onset schizophrenia. Am J Med Genet 1999;88:188–99.
[32] Nagamoto HT, Adler LE, McRae KA, Huettl P, Cawthra E, Gerhardt G, et al. Auditory P50 in schizophrenics on clozapine: improved gating parallels clinical improvement and changes in plasma 3-methoxy-4-hydroxyphenylglycol. Neuropsychobiology 1999;39:10–7.
[33] Shirazi-Southall S, Rodriguez DE, Nomikos GG. Effects of typical and atypical antipsychotics and receptor selective compounds on acetylcholine efflux in the hippocampus of the rat. Neuropsychopharmacology 2002;26:583–94.
[34] McEvoy JP, Freudenreich O, Wilson W. Smoking and therapeutic response to clozapine in patients with schizophrenia. Biol Psychiatry 1999;46:125–9.
[35] Becker J, Gomes I, Ghisolfi ES, Schush A, Ramos FL, Ehlers JA, et al. Clozapine, but not typical antipsychotics, correct P50 suppression deficit in patients with schizophrenia. Clin Neurophysiol 2004;115:396–401.
[36] Adler LE, Hoffer LD, Griffith J, Waldo MC, Freedman R. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. Biol Psychiatry 1992;32:607–16.
[37] Freedman R, Adler LE, Bickford PC, Byerley W, Coon H, Cullum CM, et al. Schizophrenia and nicotinic receptors. Harvard Rev Psychiatry 1994;179–92.
[38] Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc Natl Acad Sci USA 1997;94:587–92.
[39] Leonard S, Gault J, Moore T, Hopkins J, Robinson M, Olincy A, et al. Further investigation of a chromosome 15 locus in schizophrenia: analysis of affected sibpairs from the NIMH genetics initiative. Am J Med Genet 1998;81:308–12.
[40] Riley BP, Makoff A, Mogudi-Carter M, Jenkins T, Williamson R, Collier D, et al. Haplotype transmission disequilibrium and evidence for linkage of the CHRNA7 gene region to schizophrenia in Southern African Bantu families. Am J Med Genet 2000;96:196–201.
[41] Tsuang DW, Skol AD, Faraone SV, Bingham S, Young KA, Prabhudesai S, et al. Examination of genetic linkage of chromosome 15 to schizophrenia in a large veterans affairs cooperative study sample. Am J Med Genet 2001;105:662–8.
[42] Liu C-M, Hwu H-G, Lin M-W, Ou-Yang W-C, Lee SF-C, Fann CSJ, et al. Suggestive evidence for linkage of schizophrenia to markers at chromosome 15q13-14 in Taiwanese families. Am J Med Genet 2001;105:658–61.
[43] Xu J, Pato MT, Dalla Torre C, Medeiros H, Carvalho C, Basile VS, et al. Evidence of linkage disequilibrium between the alpha 7-nicotinic receptor gene (CHRNA7) locus and schizophrenia in Azorean families. Am J Med Genet 2001;105:669–74.
[44] Neves-Pereira M, Bassett AS, Honer WG, Lang D, King NA, Kennedy JL. No evidence for linkage of the CHRNA7 gene region in Canadian schizophrenia families. Am J Med Genet 1998;81:361–3.
[45] Curtis L, Blouin J-L, Radhakrishna U, Gehrig C, Lasseter VK, Wolyniec P, et al. No evidence for linkage between schizophrenia and markers at chromosome 15q13-14. Am J Med Genet 1999;88:109–12.
[46] Leonard S, Gault J, Hopkins J, Logel J, Vianzon R, Short M, et al. Association of promoter variants in the alpha-7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. Arch Gen Psychiatry 2002;59:1085–96.
[47] Houy E, Raux G, Thibaut F, Belmont A, Demily C, Allio G, et al. The promoter −194 C polymorphism of the nicotinic alpha 7 receptor gene has a protective effect against the P50 sensory gating deficit. Mol Psychiatry 2004;9:320–2.
[48] Court J, Spurden D, Lloyd S, McKeith I, Ballard C, Cairns N, et al. Neuronal nicotinic receptors in dementia with lewy bodies and schizophrenia: alpha-bungarotoxin and nicotine binding in thalamus. J Neurochem 1999;73: 1590–7.
[49] Freedman R, Hall M, Adler LE, Leonard S. Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry 1995;38:22–33.
[50] Marutle A, Zhang X, Court J, Piggot M, Johnson M, Perry R, et al. Laminar distribution of nicotinic receptor subtypes in cortical regions in schizophrenia. J Chem Neuroanat 2001;22:115–26.
[51] Guan Z-Z, Zhang X, Blennow K, Nordberg A. Decreased protein level of nicotinic receptor alpha-7 subunit in the frontal cortex from schizophrenic brain. Neuroreport 1999;10:1779–82.
[52] Stevens KE, Freedman R, Collins AC, Hall M, Leonard S, Marks MJ, et al. Genetic correlation of inhibitory gating of hippocampal auditory evoked response and alpha-bungarotoxin-binding nicotinic cholinergic receptors in inbred mouse strains. Neuropsychopharmacology 1996;15:152–62.
[53] Stevens KE, Wear KD. Normalizing effects of nicotine and a novel nicotinic agonist on hippocampal auditory gating in two animal models. Pharmacol Biochem Behav 1997;57:869–74.
[54] Simosky JK, Stevens KE, Adler LE, Freedman R. Clozapine improves deficient inhibitory auditory processing in DBA/2 mice, via a nicotinic cholinergic mechanism. Psychopharmacology 2003;165:386–96.
[55] Albuquerque EX, Pereira EFR, Braga MFM, Alkondon M. Contribution of nicotinic receptors to the function of synapses in the central nervous system: the action of choline as a selective agonist of alpha-7 receptors. J Physiol (Paris) 1998;92:309–16.
[56] Frazier CJ, Rollins YD, Breese CR, Leonard S, Freedman R, Dunwiddle TV. Acetylcholine activates an alpha-bungarotoxin-sensitive nicotinic current in rat hippocampal interneurons, but not pyramidal cells. J Neurosci 1998;18:1187–95.
[57] Hershman KM, Freedman R, Bickford PC. GABA-B antagonists diminish the inhibitory gating of auditory response in the rat hippocampus. Neurosci Lett 1995;190:133–6.
[58] Mexal S, Jenkins PM, Lautner MA, Iacob E, Crouch E, Stitzel J. Alpha 7 nicotinic receptor gene promoter polymorphisms in inbred mice affect expression in a cell type-specific fashion. J Biol Chem 2007;282:13220–7.
[59] Hatsukami D, Fletcher L, Morgan S, Keenan R, Ambie P. The effects of varying cigarette deprivation duration on cognitive and performance tasks. J Sub Abuse 1989;1: 407–16.
[60] Levin ED, Simon BB. Nicotinic acetylcholine involvement in cognitive function in animals. Psychopharmacology 1998;138:217–30.
[61] Rinne JO, Myllykylä T, Lönnberg P, Marjamäki P. A post-mortem study of brain nicotinic receptors in Parkinson's and Alzheimer's disease. Brain Res 1991;167–70.
[62] Schroder H, Giacobini E, Wevers A, Birtsch A, Schultz U. Nicotinic receptors in Altzheimer's disease. In: Domino EF, editor. Brain imaging of nicotine and tobacco smoking. PO Box 1491, Ann Arbor, MI 48106: Npp Books; 1995. p. 73–93.
[63] Sahakian BJ, Jones GMM. The effects of nicotine on attention, information processing, and working memory in patients with dementia of the Altzheimer type. In: Adlkofer F, Thruau K, editors. Effects of nocotine on biological systems. Basel: Birkhauser Berlag; 1991. p. 230–623.

[64] Jones GMM, Sahakian BJ, Levy R, Warburton DM, Gray JA. Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Altzheimer's disease. Psychopharmacology 1992;108: 485–94.
[65] White H Levin. Chronic four week nicotine skin patch treatment effects on cognitive performance in Altzheimer's disease. Psychopharmacology 1999;143: 158–65.
[66] Newhouse PA, Sunderland T, Tariot PN, Blumhardt CL, Weingartner H, Mellow A, et al. Intravenous nicotine in Altzheimer's disease: a pilot study. Psychopharmocology 1988;95:171–5.
[67] Parks R, Becker R, Rippey R, Gilbert D, Mathews J, Kabatatm E, et al. Increased regional cerebral glucose metabolism and semantic memory performance in Altzheimer's disease: a pilot double blind transdermal nicotine positron emission tomography study. Neuropsychol Rev 1996;6:61–79.
[68] Wilson AL, Langley LK, Monley J, Bauer T, Rottunda S, Mcfalls E, et al. Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. Pharmacol Biochem Behav 1995;51:509–14.
[69] Levin ED, Rezvani AH. Development of nicotinic drug therapy for cognitive disorders. Eur J Pharmacol 2000;393:141–6.
[70] George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, et al. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. Neuropsychopharmacology 2001;26:75–85.
[71] Sacco KA, Termine A, Seyal A, Dudas MM, Vessicchio JC, Krishnan-Sarin S, et al. Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia. Arch Gen Psychiatry 2005;62: 649–59.
[72] Levin E, Wilson WH, Rose JE, McEvoy JP. Nicotine–haloperidol interaction and cognitive performance in schizophrenics. Neuropsychopharmacology 1996;15: 429–36.
[73] Jacobsen LK, D'Souza DC, Mencl WE, Pugh KR, Skudlarski P, Krystal J. Nicotine effects on brain function and functional connectivity in schizophrenia. Biol Psychiatry 2004;55:850–8.
[74] Dépatie L, O'Driscoll GA, Holahan AL, Atkinson V, Thavundayil JX, Kin NNY, et al. Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. Neuropsychopharmacology 2002;27:1056–70.
[75] Harris JG, Kongs S, Allensworth D, Martin L, Tregellas J, Sullivan B, et al. Effects of nicotine on cognitive deficits in schizophrenia. Neuropsychopharmacology 2004;29: 1378–85.
[76] Smith RC, Singh A, Infante M, Khandat A, Kloos A. Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. Neuropsychopharmacology 2002;27:479–97.
[77] Myers CS, Robles O, Kakoyannis AN, Sherr JD, Avila MT, Blaxton TA, et al. Nicotine improves delayed recognition in schizophrenic patients. Psychopharmacology 2004;174:334–40.
[78] Sherr JD, Myers C, Avila MT, Elliot A, Blaxton TA, Thaker GK. The effects of nicotine on specific eye tracking measures in schizophrenia. Biol Psychiatry 2002;52: 721–8.
[79] Benowitz NL. Summary: risks and benefits of nicotine. In: Benowitz NL, editor. Nicotine safety and toxicity. New York: Oxford University Press; 1998. p. 185–8.
[80] Kem WR, Abbott BC, Coates RM. Isolation and structure of a hoplonemertine toxin. Toxicon 1971;9:15–22.
[81] Kem WR, Mahnir VM, Papke RL, Lingle CJ. Anabaseine is a potent agonist on muscle and neuronal alpha-bungarotoxin-sensitive nicotinic receptors. J Pharmacol Exp Ther 1997;283:979–92.
[82] Briggs CA, McKenna DG, Piattoni-Kaplan M. Human alpha-7 nicotinic acetylcholine receptor responses to novel ligands. Neuropharmacology 1995;34:583–90.
[83] De Fiebre CM, Meyer EM, Henry JC, Muraskin SI, Kem WR, Papke RL. Characterization of a series of anabaseine-derived compounds reveals that the 3-(4)-dimethylaminocinnamylidine derivative is a selective agonist at neuronal nicotinic alpha-7/125 i-alpha-bungarotoxin receptor subtypes. Mol Pharmacol 1995;47:164–71.
[84] Kem WR, Mahnir VM, Lin B, Prokai-Tartrai K. Two primary GTS-21 metabolites are potent partial agonists at alpha7 nicotinic receptors expressed in the Xenopus oocyte. Soc Neurosci Abstract 1996;22:268.
[85] Papke RL, Meyer E, Nutter T, Uteshev VV. Alpha-7 Receptor-selective agonists and modes of alpha-7 receptor activation. Eur J Pharmacol 2000;393:179–95.
[86] Stevens KE, Kem WR, Mahnir VM, Freedman R. Selective alpha-7 nicotinic agonists normalize inhibition of auditory response in DBA mice. Psychopharmacology 1998;136: 320–7.
[87] Luntz-Leybman V, Bickford PC, Freedman R. Cholinergic gating of response to auditory stimuli in rat hippocampus. Brain Res 1992;587:130–6.
[88] Radek RJ, Miner HM, Bratcher NA, Decker MW, Gopalakrishnan M, Bitner RS. Alpha4beta2 nicotinic receptor stimulation contributes to the effects of nicotine in the DBA/2 mouse model of sensory gating. Psychopharmacology 2006;187:47–55.
[89] Freedman R, Wetmore C, Stromberg I, Leonard S, Olson L. Alpha-bungarotoxin binding to hippocampal interneurons: immunocytochemical characterization and effects on growth factor expression. J Neurosci 1993;13:1965–75.
[90] O'Neill HC, Reiger K, Kem WR, Stevens KE. DMXB, an alpha7 nicotinic agonist, normalizes auditory gating in isolation-reared rats. Psychopharmacology 2003;163: 332–9.
[91] Stevens KE, Kem WR, Freedman R. Selective alpha 7 nicotinic receptor stimulation normalizes chronic cocaine-induced loss of hippocampal sensory inhibition in C3H mice. Biol Psychiatry 1999;46:1443–50.
[92] Simosky JK, Stevens KE, Kem WR, Freedman R. Intragastric DMXB-A, an alpha7 nicotinic agonist, improves deficient sensory inhibition in DBA/2 mice. Biol Psychiatry 2001;50:493–500.
[93] Swerdlow NR, Braff DL, Taaid N, Geyer MA. Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. Arch Gen Psychiatry 1994;51:139–54.
[94] Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 2001;156:234–58.
[95] George TP, Termine A, Sacco KA, Allen TM, Reutenauer E, Vessiccho JC, et al. A preliminary study of the effects of cigarette smoking on prepulse inhibition in schizophrenia: involvement of nicotinic receptor mechanisms. Schizophrenia Res 2006;87:307–15.
[96] Kumari V, Soni W, Sharma T. Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. Hum Psychopharmacol 2001;l16:321–6.
[97] Suemaru K, Yasuda K, Umeda K, Araki H, Shibata K, Choshi T, et al. Nicotine blocks apomorphine-induced

disruption of prepulse inhibition of the acoustic startle in rats: possible involvement of central nicotinic alpha7 receptors. Br J Pharmacol 2004;142:843–50.
[98] Schreiber R, Dalmus M, De Vry J. Effects of alpha 4/beta 2- and alpha 7-nicotine acetylcholine receptor agonists on prepulse inhibition of the acoustic startle response in rats and mice. Psychopharmacology 2002;159:248–57.
[99] Bowie CR, Harvey PD. Cognition in schizophrenia: impairments, determinants, and functional importance. Psychiatry Clin North Am 2005;28:613–33.
[100] Joyce EM, Roiser JP. Cognitive heterogeneity in schizophrenia. Curr Opin Psychiatry 2007;20:268–72.
[101] Tamminga CA. The neurobiology of cognition in schizophrenia. J Clin Psychiatry 2006;67:9–13.
[102] Barr RS, Culhane MA, Jubelt LE, Mufti RS, Dyer MA, Weiss AP, et al. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. Neuropsychopharmacol 2007. doi: 10.1038/sj.npp.1301423.
[103] Ciamei A, Aversano M, Cestari C, Castellano C. Effects of MK-801 and nicotine combinations on memory consolidation in CD1 mice. Psychopharmacology 2001;154:126–30.
[104] Moragrega I, Carrasco MC, Vicens Pl, Redolcat R. Spatial learning in male mice with different levels of aggressiveness: effects of housing conditions and nicotine administration. Behav Brain Res 2003;147:1–8.
[105] Puma C, Deschaux O, Molimard R, Bizot JC. Nicotine improves memory in an object recognition task in rats. Eur Neuropsychopharmacol 1999;9:23–7.
[106] Woodruff-Pak DS, Green JT, Coleman-Valencia C, Pak JT. A nicotinic cholinergic agonist (GST-21) and eyeblink classical conditioning: acquisition, retention and relearning in older rabbits. Exp Aging Res 2000;26:323–6.
[107] Young J, Finalyson K, Spratt C, Marston H, Crawford N, Kelly J, et al. Nicotine improves sustained attention in mice: evidence for involvement of the alpha7 nicotinic acetylcholine receptor. Neuropsychopharmacology 2004;29:891–900.
[108] Briggs CA, Anderson DJ, Brioni JD, Buccafusco JJ, Buckley MJ, Campbell JE, et al. Functional characterization of the novel neuronal nicotinic acetylcholine receptor ligand GTS-21 in vitro and in vivo. Pharmacol Biochem Behav 1997;57:231–41.
[109] Woodruff-Pak DS, Li Y-T, Kem WR. A nicotinic agonist (GTS-21), eye blink classical conditioning, and nicotinic receptor binding in rabbit brain. Brain Res 1994;645:309–17.
[110] Woodruff-Pak DS. Mecamylamine reversal by nicotine and by a partial alpha-7 nicotinic acetylcholine receptor agonist (GTS-21) in rabbits tested with delay eye blink classical conditioning. Behav Brain Res 2003;143:159–67.
[111] Arendash GW, Sengstock GJ, Sanberg PR, Kem WR. Improved learning and memory in aged rats with chronic administration of the nicotinic receptor agonist GTS-21. Brain Res 1995;674:252–9.
[112] Meyer E, Kuryatov A, Gerzanich V, Lindstrom J, Papke RL. Analysis of 3-(4-hydroxy, 2-methoxybenzylidene) anabaseine selectivity and activity at human and rat alpha-7 nicotinic receptors. J Pharmacol Exp Ther 1998;287:918–25.
[113] Meyer EM, De Fiebre CM, Hunter BE, Simpkins CE, Frauworth N, De Fiebre NEC. Effects of anabaseine-related analogs on rat brain nicotinic receptor binding and on avoidance behaviors. Drug Dev Res 1994;31:127–34.
[114] Nanri M, Yamamoto J, Miyake H, Watanabe H. Protective effect of GTS-21, a novel nicotinic receptor agonist, on delayed neuronal death induced by ischemia in gerbils. Jpn J Pharmacol 1998;76:23–9.
[115] Meyer EM, Tay EE, Papke RL, Meyers C, Huang G. deFiebre CM 3-[2,4-dimethoxybenzylidene]anabaseine (DMXB) selectively activates rats α7 receptors and improves memory-related behaviors in a mecamylamine-sensitive manner. Brain Res 1997;768:49–56.
[116] Kitagawa H, Takenouchi T, Azuma R, Wesnes KA, Kramer WG, Clody DE, et al. Safety, pharmacokinetics, and effects on cognitive function of multiple doses of GTS-21 in healthy, male volunteers. Neuropsychopharmacology 2003;28:542–51.
[117] Olincy A, Harris JG, Johnson LL, Pender V, Kongs S, Allensworth D, et al. An α7-nicotinic cholinergic agonist enhances cognitive function in schizophrenia. Arch Gen Psychiatry 2006;63:630–8.
[118] Gold JM, Queern C, Iannone VN, Buchanan RW. Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia I: sensitivity, reliability, and validity. Am J Psychiatry 1999;156:1944–50.
[119] Wishka DG, Walker DP, Yates KM, Reitz SC, Shaojuan J, Meyers JK, et al. Discovery of N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl furo[2,3-c]pyridine-5-carboxamide, an agonist of the α7 nicotinic acetylcholine receptor, for the potential treatment of cognitive deficits in schizophrenia: synthesis and structure-activity relationship. J Med Chem 2006;49:4425–36.
[120] Pichat P, Bergis OE, Terranova JP, Urani A, Duarte C, Santucci V, et al. SSR180711, a novel selective alpha7 nicotinic receptor partial agonist: (II) efficacy in experimental models predictive of activity against cognitive symptoms of schizophrenia. Neuropsychopharmacology 2007;32:17–34.
[121] Mullen G, Napier J, Balestra M, DeCory T, Hale G, Macor J, et al. (−)-Spiro[1-azabicyclo[2.2.2]octane-3,5′-oxazolidin-2′-one], a conformationally restricted analogue of acetylcholine, is a highly selective full agonist at the alpha-7 nicotinic acetylcholine receptor. J Med Chem 2000;43:4045–50.
[122] Olivier B, Leahy C, Mullen T, Paylor R, Groppi VE, Sarnyai Z, et al. The DBA/2J strain and prepulse inhibition of startle: a model system to test antipsychotics? Psychopharmacology 2001;156:284–90.
[123] Schreiber R, Dalmus M, De Vry J. Effects of the alpha-4/beta-2 and alpha-7 nicotine acetylcholine receptor agonists on prepulse inhibition of the acoustic startle response in rats and mice. Psychopharmacology 2002;159:248–57.
[124] Grottick A, Higgins G. Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. Behav Brain Res 2000;117:197–208.
[125] Hahn B, Sharples CG, Wonnacott S, Shoaib M, Stolerman IP. Attentional effects of nicotinic agonists in rats. Neuropharmacology 2003;44:1054–67.
[126] Adler LE, Cawthra EM, Donovan KA, Harris JG, Nagamoto HT, Olincy A, et al. Improved P50 auditory gating with ondansetron in medicated schizophrenia patients. Am J Psychiatry 2005;162:386–8.
[127] Macor J, Gurley D, Lanthorn T, Loch III J, Mack RA, Mullen G, et al. The 5-HT3 antagonist tropisetron (ICS 205-930) is a potent selective alpha-7 nicotinic receptor partial agonist. Bioorg Med Chem Lett 2001;11:319–21.
[128] Papke RL, Schiff HC, Jack BA, Horenstein NA. Molecular dissection of tropisetron, an alpha-7 nicotinic acetylcholine receptor-selective partial agonist. Neurosci Lett 2005;378:140–4.
[129] Koike K, Hashimoto K, Takai N, Shimizu E, Komatsu N, Watanabe H, et al. Tropisetron improves deficits in auditory P50 suppression in schizophrenia. Schizophrenia Res 2005;76:67–72.