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Treating schizophrenia symptoms with an $\alpha 7$ 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 nicotinic 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 $\alpha 7$ 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 $\alpha 7$ subtype of the nicotinic cholinergic receptors in these processes. Rodent studies also demonstrated the efficacy of a selective partial $\alpha 7$ 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 $\alpha 7$ nicotinic activity may have utility in treating certain symptoms of schizophrenia.

Keywords

Schizophrenia; nicotinic receptors; DMXBA; P50 auditory evoked potential; cognitive deficits; nicotine

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 receptors system.

$\alpha 7$ 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

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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. 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 (Figure 1). 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 [4,5,6,7] 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[9,10,11,12,13,14,15]. 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[17,18,19,20]. Others have proposed that smoking alleviates symptoms of nicotine withdrawal or neuroleptic-induced side effects[21, 22,23,24]. Finally, smoking may be an attempt to improve cognition and sensory gating[25, 26,27].

Nicotine appears to have a positive effect on P50 inhibition in schizophrenia[27]. When people with schizophrenia who have been withdrawn from nicotine smoke cigarettes, they are able to temporarily filter stimuli. However within approximately 30 minutes, 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[28]. 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[29,30,31,32]. People with schizophrenia treated with clozapine exhibit normalization of their P50 ratio coincident with improvement in their clinical symptoms[33]. Clozapine, which releases acetylcholine in the hippocampus[34], 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 [35,36]. Clozapine also has the property of 5HT₃ antagonism, which activates nicotinic cholinergic receptors. Nicotine gum and physostigmine also improve P50 suppression in relatives of people with schizophrenia[37]. Administration of high dose nicotine with 10 mg of mecamylamine, a high affinity $\alpha 4\beta 2$ nicotinic cholinergic receptors antagonist still produces improvement in P50 suppression in schizophrenia[38](Figure 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 $\alpha 7$ nicotinic cholinergic receptors.

Additional independent evidence for involvement of the $\alpha 7$ cholinergic receptor in the P50 auditory evoked potential 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 $\alpha 7$ gene with a lod score of 5.3, $\Theta = 0.0$ [39]. Linkage of this region to schizophrenia was further replicated in families from the NIMH Schizophrenia Genetics Initiative[40] and in other studies [41,42,43,44], but there have also been some negative studies in this region[45,46]. 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[47,48]. Furthermore, the presence of a SNP in the 15q14 gene *CHRNA7* 5'

core promoter is significantly associated with P50 suppression deficits[47]. 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[47,48]. 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 $\alpha 7$ nicotinic cholinergic receptor binding has been noted in the reticular nucleus of the thalamus, the hippocampus, the cingulate cortex and the frontal lobe regions[49,50,51, 52].

A similar deficit in auditory 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[53] (Figure 3). Studies have shown that the auditory gating improves in the DBA/2 mouse with nicotine administration[54], just as it does in schizophrenia patients[27]. Additionally, similar effects were found for clozapine in both the DBA/2 mouse[55] and schizophrenia patients[33]. The mechanism of auditory gating has been clarified through the use of these animal models. The activation of the $\alpha 7$ cholinergic receptors release GABA from GABAergic interneurons[56, 57] which then act on GABA_B receptors which activates that decrease the release of glutamate thus preventing hippocampal neurons from responding to the second stimulus in the P50 paradigm [58]. Nitric oxide acts as a second messenger to prolong the effect of the $\alpha 7$ nicotinic cholinergic receptor stimulation. Additionally, a promoter region polymorphism exists between the CH3 and the DBA/2 mouse strains[59] which model the polymorphisms observed in the human promoter region[39]. Thus, the DBA/2 mouse represents a useful model of the auditory gating deficit in schizophrenia from both the phenotypic and genotypic standpoint. The DBA/2 mouse also shows a reduction in the number of hippocampal $\alpha 7$ nicotinic cholinergic receptors [60] similar to what is observed in humans with schizophrenia[50].

$\alpha 7$ 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[61]. 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[62]. In Alzheimer's disease, where nicotinic cholinergic receptors are known to be decreased in the cortex and hippocampus[63,64], nicotine injections or nicotine skin patches significantly improve attention, learning and memory[65,66,67,68,69,70]. Similarly, in adults with attention deficit disorder, nicotine skin patch reduces clinical symptoms and increases reaction time, but does not improve errors of omission in the Continuous Performance Test[71]. The effects of nicotine on neuropsychological measures in persons with schizophrenia, unlike the effects on the P50 auditory evoked potential less are conclusive. In smokers with schizophrenia, with abstinence from nicotine, working memory is decreased [72,73]. If nicotine is then reinitiated by smoking, working memory deficits are normalized [73]. 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[74]. In another study, the nicotine patch also improved auditory working memory, attention, complex reaction times but not simple reaction times [75,76,74]. Nicotine gum 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[77]. Finally, nicotine nasal spray enhances verbal memory[78], visuospatial delayed recognition[79] and complex reaction times but has no effect on simple reaction times attention or working memory[74,80,79]. 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.

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[81]. 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[82,83]. DMXBA is a partial agonist at the $\alpha 7$ nicotinic cholinergic receptor [84,85] and a weak competitive antagonist at the $\alpha 4\beta 2$ nicotinic cholinergic receptors and 5HT₃ receptors[86,87]. The first step in testing of this compound was to administer DMXBA in DBA/2 mice. This compound produced a dose-dependent improvement in auditory gating in this model (Figure 4A) which occurred through a selective reduction in the response to the second stimulus (Figure 4B) [88]. This pattern is in concert with what is now known regarding nicotinic modulation of the 2 evoked potentials, that is that modulation of the response to the second stimulus is mediated by $\alpha 7$ nicotinic cholinergic receptor [89] while the response to the first stimulus is mediated, in part, by $\alpha 4\beta 2$ nicotinic cholinergic receptor [90]. Thus, increased stimulation of the limited numbers of hippocampal $\alpha 7$ nicotinic cholinergic receptor with DMXBA in this mouse strain increases firing of the interneurons, on which they reside[91], which in turn inhibits firing of a subpopulation of pyramidal cells in response to the second stimulus. Antagonism of the $\alpha 4\beta 2$ receptors with mecamylamine blocks any stimulation by endogenous acetylcholine, thus inhibiting increases in the response to the first stimulus, as is commonly observed with non-selective agonists such as nicotine[54]. The improvement in auditory gating has been replicated in isolation-reared rats which show deficient auditory gating[92], in C3H chronically treated with cocaine, which also show deficient auditory gating[93] and after oral administration of DMXA in DBA/2 mice[94].

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 [95]. Schizophrenia patients do not show normal PPI[96], but smoking improves the deficit [97,98]. In rodent studies, nicotine improves PPI in a model of deficient schizophrenia-like PPI[99]. Administration of DMXBA also improves deficient PPI[100].

Finally, cognitive and attentional deficits are a recognized symptom class in schizophrenia [101,102,103] which can be improved with nicotine administration[104,76,77,78]. 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[105,106,107,108,109]. DMXBA improves monkey performance on a delayed matching to sample task, an effect that persists for 24 hours after drug administration[110]. The administration of DMXBA improves eyeblink classical conditioning acquisition in older rabbits who have lost cholinergic neurons[111] Mecamylamine, an $\alpha 4\beta 2$ 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.[112]. DMXBA improves one-way active avoidance, Lashley III maze testing, and 17 arm radial maze test performance in aged rats[113,114]. Passive avoidance deficits are normalized in rats[115] and ischemia-induced hippocampal cell death and impaired passive avoidance performance in gerbils are prevented by treatment with DMXBA[116]. DMXBA also improves performance on the Morris water maze[117].

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[118]. 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 1-1.2h 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[118].

As this agent appeared safe and promising in enhancing cognition, DMXBA was studied in schizophrenia to prove that the $\alpha 7$ 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 [119]. 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 mg or 75 mg) followed two hours later by a half dose (75 mg 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, identical in appearance, randomly on 3 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[120], 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; Figure 5; [119]. 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[77]. 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; Figure 6; [119]. Increased inhibition of the P50 response during DMXBA is consistent with the hypothesized agonist effect on $\alpha 7$ 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.

Other Potential Nicotinic Targets

A series of other potential 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 -diazabicyclo[3.2.2]nonane-4-carboxylic acid 4-pyridin-2-yl-phenyl ester at Pfizer Inc., and a N-[(3R)-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[121]. 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 $\alpha 7$ nicotinic cholinergic receptor partial agonist from Sanofi-Adventis, enhances episodic memory in the object recognition task in rats preadministered methyllycaconitine, an $\alpha 7$ nicotinic cholinergic receptor antagonist and in mice. However, when administered to $\alpha 7$ knockout mice, there is not enhancement of long-term episodic memory[122]. AR-R 17779, an AstraZeneca product, is an acetylcholine analogue with full agonist properties at the $\alpha 7$ nicotinic cholinergic receptor. This compound does not enhance the inhibition of startle in DBA/2 mice[123,124,125] or improve accuracy and speed of response on a five-choice serial reaction time[126,127]. ABT-418, has some agonist properties at the $\alpha 7$ nicotinic cholinergic receptors, but is a less potent agonist than nicotine[128] 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[54].

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 5HT₃ receptors antagonism. Ondansetron enhances P50 auditory suppression in persons with schizophrenia two hours after acute dosing [129]. Tropisetron, also a 5HT₃ antagonist marketed outside the United States as an antinausea drug, also has efficacy as an $\alpha 7$ nicotinic cholinergic receptor agonist[130,131]. Low dose tropisetron increased the inhibition of the P50 auditory evoked potential differentially in non-smokers with schizophrenia[132], with no effect seen on smokers with schizophrenia. Consistent with a previous finding of the effect in smokers,[77] the authors proposed that the nicotinic cholinergic receptors were chronically desensitized and that additional nicotinic agonism was blocked in smokers.

Discussion

The $\alpha 7$ 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 extraction of nicotine and heavy smoking[16,11]. 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[54,27]. This P50 auditory evoked potential deficit is linked to 15q14 at a polymorphic marker < 120 kb from the $\alpha 7$ gene [39]. Postmortem studies which demonstrate decreased $\alpha 7$ nicotinic cholinergic receptor binding have been noted in the reticular nucleus of the thalamus, the hippocampus, the cingulate cortex and the frontal lobe regions[49,50,51,52]. Nicotine has brief cognitive-enhancing effects in schizophrenia [74,75,76,77,78,79,80]. 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. [81]. 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 $\alpha 7$ nicotinic cholinergic receptor [84,85] and a weak competitive antagonist at the $\alpha 4\beta 2$ nicotinic cholinergic receptor and 5HT₃ receptors [86,87,119]. Additionally, P50 auditory gating was also improved [119]. 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 hours, 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.

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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Figure 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 responses of the conditioning amplitude. (Adapted from Adler et al 1990.)

Figure 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 $\alpha 2\beta 4$ 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).

Figure 3.

Auditory evoked potentials in response to identical paired stimuli in 2 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. . (From Stevens et al 1996).

Figure 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 auditory gating in the DBA/2 mouse, a model of schizophrenia-like deficits in auditory gating. DMXBA was administered as indicated by the arrows labeled injection. Asterisks indicate ratios that are significantly different from vehicle. 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 subcutaneous and recordings obtained at 5 minute intervals. At 40 minutes, when the responses were back to baseline levels, a second identical injection was administered and recordings were obtained for an additional 40 minutes. Filled circles indicate mean conditioning amplitude. Open circles indicate mean test amplitude. Asterisks indicate amplitudes that are significantly different from vehicle (Adapted from Stevens et al 1998).

Figure 5.

Auditory evoked responses of a subject with schizophrenia. Stimuli were a conditioning auditory stimulus and an identical test stimulus, delivered 500 msec 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 μ V, and horizontal is 50 ms. (Adapted from Olinicy et al. 2006).

Figure 6. 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 Olinicy et al. 2006).