Published in final edited form as:

Eur J Pharmacol. 2013 February 28; 702(0): 269–274. doi:10.1016/j.ejphar.2013.01.056.

Improvement of attentional function with antagonism of nicotinic receptors in female rats

Edward D. Levin, Marty Cauley, and Amir H. Rezvani

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Abstract

Nicotinic agonists have been shown in a variety of studies to improve cognitive function. Since nicotinic receptors are easily desensitized by agonists, it is not completely clear to what degree receptor desensitization or receptor activation are responsible for nicotinic agonist-induced cognitive improvement. In the current study, the effect of the neuronal nicotinic cholinergic $\alpha 4\beta 2$ receptor antagonist dihydro- β -erythroidine (DH β E) and the $\alpha 7$ nicotinic receptor antagonist methyllycaconitine (MLA) on attentional function was determined. Adult female Sprague-Dawley rats were trained on the visual signal detection task. They were required to discriminate whether or not a light signal occurred on a trial and respond with a lever press on one side after a signal and the opposite side after the absence of a signal in order to receive a food pellet reinforcer. Acute administration of the $\alpha 4\beta 2$ antagonist DH β E improved attentional function either alone or in reversing the attentional impairment caused by the NMDA glutamate antagonist dizocilpine (MK-801). Acute administration of MLA also significantly attenuated the dizocilpine-induced attentional impairment. In previous research we have shown that the $\alpha 4\beta 2$ nicotinic desensitizing agent and partial agonist sazetidine-A also was effective in reversing dizocilpine-induced attentional impairments on the signal detection task and that low doses of the general nicotinic antagonist mecamylamine improved learning and memory. The current studies indicate that blockade of nicotinic receptors can effectively attenuate attentional impairments. Development of drugs that provide a net decrease in nicotinic receptor activity either through antagonism or desensitization could be worth exploring for beneficial effects for treating cognitive impairments.

Index words

Nicotinic; Attention; Antagonist; $\alpha 4\beta 2$; $\alpha 7$

1. Introduction

Nicotinic cholinergic receptors are found throughout the nervous system and are involved in a variety of behavioral functions. Some actions of nicotine, like its promoting cigarette smoking, are adverse. Other effects, like nicotine-induced improvement in cognitive function (Levin et al., 2006; Rusted et al., 2008), present opportunities for therapeutic treatment. Nicotinic receptor systems have been found to be important for a variety of

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Address Correspondence to: Edward D. Levin, Ph.D., Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 104790, Durham, NC, 21170, USA.

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cognitive functions including prominently memory and attention (Levin et al., 2006). Nicotinic treatments hold promise for syndromes of cognitive dysfunction such as Alzheimer's disease, attention deficit hyperactivity disorder (ADHD) as well as the cognitive deficits in other disorders such as schizophrenia and Parkinson's disease (Levin and Rezvani, 2000; Newhouse et al., 1997; Rezvani and Levin, 2001). For the main part, studies have found that nicotine and other nicotinic agonists improve cognitive function but, there are also reports that nicotine does not improve cognitive performance or can impair it and in some cases nicotinic antagonist treatment can improve cognitive performance (for review see Levin et al., 2006). Nicotine has potent actions of desensitizing nicotinic receptors (Ochoa et al., 1989; Paradiso and Steinbach, 2003). Desensitization of nicotinic receptors has been suggested as a useful avenue for drug development (Buccafusco et al., 2009; Picciotto et al., 2008).

Sazetidine-A, a nicotinic $\alpha 4\beta 2$ receptor desensitizing agent, was found in our earlier studies to significantly improve attentional function in terms of reversing attentional impairments caused by the NMDA glutamate antagonist dizocilpine (MK-801) and the muscarinic cholinergic antagonist scopolamine (Rezvani et al., 2011; Rezvani et al., 2012a). However, sazetidine-A also has an agonist effect at one of the configurations of $\alpha 4\beta 2$ receptors (Zwart et al., 2008), leaving open the possibility that it may have been this agonist effect rather than the net antagonist effect from desensitization that was responsible for the attentional improvement. The goal of the current study was to determine whether an outright $\alpha 4\beta 2$ nicotinic antagonist would have a similar effect for reversing dizocilpine-induced attentional impairments. It was hypothesized that the $\alpha 4\beta 2$ nicotinic receptor antagonist, dihydro- β -erythroidine (DH β E) would attenuate attentional impairments caused by dizocilpine.

The effects of the $\alpha 7$ antagonist methyllycaconitine (MLA) were also assessed to compare with the effects of $\alpha 4\beta 2$ blockade and to determine whether previous findings that $\alpha 7$ agonists improve attentional function (Leiser et al., 2009; Rezvani et al., 2009a; Sydserff et al., 2009; Wallace et al., 2011) may have been due to the desensitization of $\alpha 7$ receptors caused by these agonists providing net antagonist effects. Recently, Hahn et al. found that low doses of MLA effectively improve attentional function of rats (Hahn et al., 2011). The interactions of both antagonists with nicotine were assessed to determine the interactions of the antagonists with nicotine, which both activates and desensitizes both $\alpha 7$ and $\alpha 4\beta 2$ nicotinic receptors.

2. Materials and methods

2.1. Subjects

Adult female Sprague-Dawley rats (Taconic Farms, Germantown, NY, USA) were used in these experiments (N=23). Rats were housed in groups of three in plastic cages with wood shavings in a vivarium with 12L:12D reversed light schedule (light on at 7:00 PM). The rats had unrestricted access to drinking water but were fed daily after testing such that their weights were kept at approximately 85% of free-feeding values. Their mean weight was 243 ± 2 g (mean $\pm$ S.E.M.). The treatment and care of the animals was carried out under an approved protocol of the Animal Care and Use Committee of Duke University in an AAALAC-approved facility.

2.2. Experimental Protocol

There were two groups of rats trained, one for testing of DH β E and the other for testing of MLA. In DH β E study rats (N=11) were first tested for the acute dose-effect function of DH β E (0, 1, 2, 4 and 8 mg/kg) with the doses given in a repeated measures counterbalanced order. Then, the same rats were tested for the interactions of DH β E (8 mg/kg) with nicotine

(0.025 and 0.05 mg/kg) and dizocilpine (0.05 mg/kg) with the dose combinations given in a repeated measures counterbalanced order. In the MLA study a separate group of rats (N=12) were tested for the acute dose-effect function of MLA (0, 1, 2, 4, and 8 mg/kg) with the doses given in a repeated measures counterbalanced order. Then, the same rats were tested for the interactions of MLA (8 mg/kg) with nicotine (0.025 and 0.05 mg/kg) and dizocilpine (0.05 mg/kg) with the dose combinations given in a repeated measures counterbalanced order. For all parts of the study drug injections (sc) were made in a volume of 1 ml/kg, 30 min. before the beginning of the testing for attentional function. At least two days elapsed between injections given in a counterbalanced order.

2.3 Drug Preparation

All drugs were prepared in saline solution. DH β E, MLA, nicotine and dizocilpine were purchased from Sigma (St. Louis, MO, USA). All doses are referred to the salt and were injected subcutaneously as 1 ml/kg. The pH of the injected solutions was adjusted to 7. All experiments were carried out during the dark phase of the dark-light cycle. All animals in each group received all treatments.

2.4. Visual Signal Detection Task

Each chambers was equipped with a signal light, a house light, two retractable levers, a food cup (Coulbourn Instruments, Lehigh Valley, PA, USA) a white noise generator (Med Associates Inc., Georgia, VT, USA) and a food cup. The white noise generator was used to help screen out extraneous noises which may have inadvertently distracted the subjects. The two retractable levers were located on both sides of the food cup 13 cm apart and 2.5 cm above the floor of the chamber. The levers were inserted simultaneously horizontally 2.5 cm into the chamber. The signal, or cue light, was located above the food cup at the center of the front panel 28 cm above the floor of the chamber. A signal consisted of 500-ms increase in the brightness of the signal light to levels of 0.027, 0.269 and 1.22 lux above a background illumination of 1.2 lux (Rezvani et al., 2011).

Rats were trained to perform a visual signal detection task (Bushnell, 1998; Bushnell et al., 1997). Animals were tested every day except weekends and holidays. The task was conducted in daily 240-trial sessions approximately 45 min in duration. Two trial types, “signal” and “blank,” were presented in equal number in each session in groups of 4 (2 signal and 2 blank, in random order) at each of the three signal intensities. Each signal trial included a pre-signal interval, the signal (cue light), and a post-signal interval. Following the signal, a post-signal interval of 2, 3, or 4 s (selected randomly) occurred. Blank trials were presented identically, except the signal light was not present.

A trial began with both levers retracted from the chamber, then both levers were inserted into the chamber simultaneously at the end of the post-signal interval. The levers were both retracted simultaneously when one was pressed or if 5 s passed without a press. Every correct response (i.e. a press on the signal lever in a signal trial or a press on the blank lever in a blank trial) was followed by the illumination of the food cup and delivery of one 20-mg food pellet. After each incorrect response (i.e. a press on the signal lever in a blank trial or a press on the blank lever in a signal trial) or response failure, the rat received a 2 s period of darkness (time out). If no press occurred, a response failure was recorded and the trial was not repeated.

There were two measures of choice accuracy. “Hits” were defined as correct responses on signal trials, while “correct rejections” were counted as correct responses on blank trials. Both hit and correct rejection lead to delivery of a pellet. Percent hit = (number of hits / total number of responses on signal trials) $\times$ 100 and percent correct rejection = (number of correct

rejections / total number of responses on blank trials)×100. Response latency was defined as the time elapsed between insertion of the levers and the first lever press by the rat. A response omission was recorded if the rat did not press a lever within 5 s after insertion of the levers. Increase in hit and/or correct rejection was an indicative of enhanced attention and increase in response omission suggested the opposite. Each dependent variable was subjected to an independent analysis of variance (Superanova/Statview, SAS, Cary, NC, USA). Significant interactions were followed by tests of simple main effects. The threshold for significance was set at $P < 0.05$.

2.5. Data Analysis

Analysis of variance was used to assess the statistical significance of the results. A within subjects, repeated measures design was used. The within subjects factors were dizocilpine dose (0 and 0.0625 mg/kg), MLA or DH β E dose (0 or 8 mg/kg) and nicotine dose (0, 0.025, and 0.05 mg/kg). The percent correct data (percent hit and percent correct rejection), response latency and the number of non-response trials were the dependent measures. Interactions of $P < 0.10$ were followed up by tests of the simple main effects as recommended by Snedecor and Cochran (Snedecor and Cochran, 1967). The threshold for significance was always $P < 0.05$ (two-tailed).

3. Results

3.1. DH β E Dose-Effect Function

The DH β E dose-effect function study showed a significant ($F(4,40)=4.72$, $P < 0.005$) main effect of DH β E on total percent correct (hit + correct rejection). Planned comparisons of each dose level vs control showed that all DH β E doses caused significantly higher than control performance (Table 1). There was also a significant ($F(4,40)=5.12$, $P < 0.005$) DH β E×trial type interaction. Tests of the simple main effects of control vs. each DH β E dose for hit and correct rejection trials showed that all of the doses caused significant ($P < 0.0005$) improvements in percent hit performance (Control=73.5±2.3; 1 mg/kg=82.3±1.7; 2 mg/kg=81.4±2.2; 4 mg/kg=80.3±2.1; 8 mg/kg=81.1±2.4) and none of the doses showed significant improvements for percent correct rejection performance. DH β E did not significantly affect response latency or the number of non-response trials.

3.2. MLA Dose-Effect Function

The MLA dose-effect function study did not show a significant main effect of drug dose on total percent correct (hit and correct rejection) (Table 1). There was an interaction of MLA×trial type ($F(4,40)=2.40$, $P < 0.07$), which was followed-up by tests of the simple main effects of MLA for each trial type. Planned comparisons of each dose level to control for percent hit and percent correct rejection showed that the 1 mg/kg MLA dose (80.6±1.7) caused as significant ($P < 0.05$) decrease in percent hit relative to control (84.8±1.7). None of the other simple main effects comparisons for percent hit or percent correct rejection were significant for MLA. Like DH β E, MLA did not significantly affect response latency or the number of non-response trials.

3.3. DH β E Interactions with Dizocilpine and Nicotine

The 8 mg/kg DH β E dose was used in the study of the reversal of the dizocilpine-induced deficits even though the 1 mg/kg dose caused a robust improvement in the dose-effect study, because it was thought that additional drug effect may be required to counteract the impairment rather than to improve performance from an unimpaired state. The main effect of dizocilpine was significant ($F(1,12)=13.03$, $P < 0.005$) with performance decreasing from 83.8±1.1 without dizocilpine to 79.7±1.4 with dizocilpine. The interaction of

DH β E $\times$ nicotine was significant ($F(2,24)=3.92$, $P < 0.05$). Tests of the simple main effects showed that the addition of 0.05 mg/kg nicotine to 8 mg/kg of DH β E significantly ($P < 0.005$) reduced accuracy relative to DH β E alone (Fig. 1). The three-way interaction of DH β E $\times$ dizocilpine $\times$ nicotine was significant ($F(2,24)=3.54$, $P < 0.05$). Tests of the simple main effects showed that dizocilpine caused a significant ($P < 0.005$) impairment in total percent correct relative to vehicle control. DH β E (8 mg/kg) co-administration with dizocilpine (0.0625 mg/kg) significantly ($P < 0.025$) reduced the dizocilpine-induced impairment in percent correct (Fig. 1). Interestingly, the addition of nicotine (0.05 mg/kg) to DH β E significantly ($P < 0.0005$) reduced the ameliorative effect of DH β E in reversing the dizocilpine-induced impairment in percent correct (Fig. 2).

Response latency was significantly ($F(1,12)=23.32$, $P < 0.0005$) increased by dizocilpine as a main effect, rising from 103.3 ± 3.4 ms without dizocilpine to 172.6 ± 8.2 ms with dizocilpine. There was a significant dizocilpine $\times$ nicotine interaction ($F(2,24)=8.22$, $P < 0.005$). Nicotine co-treatment aggravated the dizocilpine-induced increase in response latency. Dizocilpine without nicotine caused an average response latency of 156.4 ± 8.5 ms compared with a latency of 107.0 ± 6.2 without dizocilpine or nicotine ($P < 0.0005$), while dizocilpine with the higher dose of 0.05 mg/kg of nicotine increased response latency further to 197.2 ± 18.0 ($P < 0.001$). There was a significant main effect of DH β E treatment ($F(1,12)=4.97$, $P > 0.05$) reducing non-response trials from 9.23 ± 1.95 without DH β E to 5.88 ± 1.48 with DH β E. The number of non-response trials was significantly ($F(1,12)=13.83$, $P < 0.005$) increased by dizocilpine treatment rising from 2.1 ± 0.3 without dizocilpine to 13.0 ± 2.3 with dizocilpine.

3.4. MLA Interactions with Dizocilpine and Nicotine

The main effect of MLA was significant ($F(1,11)=17.59$, $P < 0.005$) with the rats averaging $80.2\pm1.5\%$ correct without MLA and $84.7\pm1.3\%$ with MLA (8 mg/kg). The main effect of dizocilpine was significant ($F(1,11)=24.41$, $P < 0.0005$) with the rats averaging $87.6\pm0.5\%$ correct without dizocilpine and $77.3\pm1.8\%$ correct with dizocilpine (0.0625 mg/kg). The MLA $\times$ dizocilpine interaction was significant ($F(1,11)=19.35$, $P < 0.005$). Tests of the simple main effects showed that dizocilpine caused a significant reduction in percent correct ($P < 0.0005$) and that MLA co-administration significantly ($P < 0.0005$) attenuated this impairment (Fig. 3). Figure 4 shows the corresponding data for MLA as was shown for DH β E in figure 2. Like DH β E, MLA attenuated the dizocilpine-induced impairment, but unlike DH β E the addition of nicotine did not attenuate the beneficial effect of MLA of reversing the dizocilpine-induced accuracy impairment. The four-way interaction of MLA $\times$ dizocilpine $\times$ nicotine $\times$ error type ($F(2,22)=2.99$, $P < 0.08$) prompted further analysis of the simple main effects of drug effects within this interaction. With percent hit, the addition of 0.05 mg/kg of nicotine to 0.0625 mg/kg of dizocilpine caused a significant decline ($P < 0.025$) relative to dizocilpine alone. The addition of MLA to either the combination of 0.025 mg/kg nicotine + 0.0625 mg/kg dizocilpine ($P < 0.025$) or 0.05 mg/kg nicotine + 0.0625 mg/kg dizocilpine ($P < 0.001$) improved hit accuracy relative to these conditions without MLA. With percent correct rejection, 0.0625 mg/kg of dizocilpine caused a significant ($P < 0.0005$) impairment relative to vehicle. The dizocilpine-induced impairment in correct rejection was significantly attenuated by either 0.05 mg/kg of nicotine ($P < 0.05$) or 8 mg/kg of MLA ($P < 0.005$) (Fig. 5). Figure 6 shows that nicotine (0.05 mg/kg) significantly ($P < 0.05$) attenuated the attentional impairment caused by dizocilpine ($P < 0.0005$). MLA (8 mg/kg) also significantly ($P < 0.005$) attenuated the dizocilpine-induced impairment. Nicotine co-treatment with MLA was not found to significantly alter each other's effects.

Response latency was significantly shortened by MLA (Control= 197.4 ± 10.9 , MLA= 162.9 ± 9.1) with a significant main effect ($F(1,11)=10.92$, $P < 0.01$). Dizocilpine lengthened response latency as evidenced by a significant main effect ($F(1,11)=17.67$, $P <$

0.005) with a mean response latency with no dizocilpine of 141.2 ± 7.2 ms and with dizocilpine 219.2 ± 10.7 . There was also a significant interaction of MLA $\times$ dizocilpine ($F(1,11)=8.95$, $P < 0.05$). The mean latencies were: no MLA and no dizocilpine $=147.0 \pm 11.0$, MLA and no dizocilpine $=135.4 \pm 9.5$, no MLA and dizocilpine $=247.9 \pm 14.6$ and MLA and dizocilpine $=190.5 \pm 14.4$ ms. Tests of the simple main effects found the dizocilpine significantly ($P < 0.0005$) increased response latency and co-administration of MLA with dizocilpine significantly ($P < 0.0005$) attenuated this effect. The number of non-response trials was significantly ($F(1,11)=12.94$, $P < 0.005$) decreased by MLA from 14.8 ± 2.4 without MLA to 8.0 ± 1.7 with MLA. There was also a significant ($F(1,11)=10.18$, $P < 0.01$) main effect of dizocilpine increasing the number of non-response trials from 4.7 ± 1.1 without dizocilpine to 18.0 ± 2.6 with dizocilpine. There was a significant MLA $\times$ dizocilpine interaction ($F(1,11)=32.66$, $P < 0.0005$) with MLA co-treatment reducing the number of non-response trials from 24.9 ± 4.1 with dizocilpine to 11.1 ± 3.0 with dizocilpine + MLA ($P < 0.0005$).

4. Discussion

In these studies, both the $\alpha 4\beta 2$ antagonist DH β E and the $\alpha 7$ antagonist MLA produced improvements in attentional performance on the visual signal detection task. The effects of these nicotinic antagonists were similar in reversing the attentional impairment caused by the NMDA glutamate antagonist dizocilpine (MK-801). However, their effects differed with regard to their actions when given alone and their particular interactions with nicotine. These results demonstrate conditions under which nicotinic antagonist treatment can improve attentional function.

In the dose-effect studies, the $\alpha 4\beta 2$ antagonist DH β E significantly improved choice accuracy over the entire dose range of 1–8 mg/kg, but the $\alpha 7$ antagonist MLA did not produce improved attentional performance over this range, although this may have been related to more accurate performance in the vehicle condition in the MLA compared to the DH β E study. In terms of reversing attentional deficits caused by dizocilpine, both DH β E and MLA showed effects of reversing the attentional impairment caused by this NMDA glutamate antagonist. DH β E significantly attenuated the overall choice accuracy impairment caused by dizocilpine. This effect was attenuated by co-administration of nicotine. MLA also significantly attenuated the overall choice accuracy impairment caused by dizocilpine. However, this effect was not attenuated by co-administration of nicotine. In the MLA study, percent hit was impaired when nicotine was given together with dizocilpine compared with dizocilpine alone. This was significantly reversed by co-administration of MLA. In contrast, percent correct rejection was dramatically impaired by dizocilpine alone, an effect that was significantly attenuated by co-administration of either nicotine (0.05 mg/kg) or MLA (8 mg/kg). These two treatments (MLA and nicotine) when co-administered did not produce additive effects in attenuating the dizocilpine-induced impairment.

We have previously found nicotine to have differential interactive effects with dizocilpine on percent hit and percent correct rejection (Rezvani and Levin, 2003b). As in the current study, in that earlier study we found that nicotine attenuated the dizocilpine-induced correction rejection impairment, but that nicotine co-administration with dizocilpine caused a greater impairment. In another more complex study of nicotine and dizocilpine interactions with the antipsychotic drug clozapine we did see nicotine to effectively attenuate dizocilpine-induced impairment in percent hit performance (Rezvani et al., 2008). The crucial difference in that study may have been the intermittent administration of the antipsychotic drug clozapine, which also reverses dizocilpine-induced percent hit impairments.

The beneficial effect of DH β E in reversing dizocilpine-induced attentional impairment resembles the reversal of dizocilpine by the α 4 β 2 desensitizing agent sazetidine-A on the same visual signal detection task (Rezvani et al., 2011). We found sazetidine-A to effectively reverse both the dizocilpine-induced impairments in percent hit and percent correct rejection. Because sazetidine-A has both desensitizing and mixed agonist effects at α 4 β 2 receptors, it was uncertain from that study which effect was responsible for its attentional improvement. In the current study was conducted to determine whether it was the net antagonist effects of desensitization that produced the therapeutic effect or to partial agonist action. Thus, we used the outright antagonist DH β E. This study also extended the previous study by assessing the effect of α 7 blockade with MLA. The current studies were conducted to determine if the effect of sazetidine-A was due to the net antagonist desensitizing effect or due to the partial agonist effect.

For comparison the effect of α 7 nicotinic receptor blockade with MLA was assessed. Since α 7 nicotinic receptors are easily desensitized it may be the case that some of the beneficial effects of α 7 nicotinic agonists may derive from the net desensitization of α 7 nicotinic receptors. Given the inverted U-shaped dose-effect curves often seen with cognitive enhancing drugs and studies showing apparent blockade of the nicotinic agonist effect of cognition with the corresponding antagonist may not be as simple as first appears. For example, Thomsen et al. demonstrated a beneficial cognitive effect of the nicotinic α 7 agonist SSR180711 with an inverted U-shaped dose-effect function reversing the adverse effects of NMDA glutamate blockade with PCP (Thomsen et al., 2009). In a follow-up experiment, they showed that the beneficial action of the most effective SSR180711 dose was reversed with the α 7 antagonist MLA. This result could be explained as discussed in the article that MLA blocked the agonist effect of SSR180711. However, another possible explanation is that SSR180711 may have its beneficial action expressed via desensitization and net antagonist effect on α 7 receptors. The additional antagonist action provided the MLA may have extended the α 7 underactivity past the optimal level down the higher end of the inverted U-shaped dose-effect curve.

This signal detection operant task of sustained attention developed by Bushnell (Bushnell, 1995) has been used in a variety of studies. These studies have demonstrated that blockade of muscarinic acetylcholine receptors with scopolamine, blockade of NMDA glutamate receptors (Bushnell et al., 1997; Rezvani et al., 2011; Rezvani et al., 2012b), antipsychotic drug haloperidol (Rezvani and Levin, 2004), alcohol (Rezvani and Levin, 2003a) and toxicants such as toluene (Oshiro et al., 2007), perchloroethylene (Oshiro et al., 2004; 2008) and chlorpyrifos (Samsam et al., 2005) can impair attention which can be detected by this task. This signal detection task has also been found to be sensitive to the attentional improving effects of the ADHD medication methylphenidate (Ritalin®) (Rezvani et al., 2009b), the Alzheimer's medication donepezil (Rezvani et al., 2012b), as well as nicotine (Rezvani and Levin, 2003b) and nicotinic agonists (McGaughy et al., 1999; Rezvani et al., 2012b; Rezvani et al., 2009a).

Attention is not the only cognitive function to be improved by nicotinic antagonist treatment. We have also found that low doses of the nicotinic antagonist mecamylamine can improve learning (Levin and Caldwell, 2006) and memory (Levin et al., 1993). Others have also found instances of nicotinic antagonist induced cognitive improvement. Picciotto and Buccafusco both concluded that net decreases in nicotinic stimulation could provide clinically beneficial effects including cognitive improvement (Buccafusco et al., 2009; Picciotto et al., 2008). In a clinical study low doses of mecamylamine were also been found to significantly improve memory in adults with ADHD (Potter et al., 2009).

The specific brain systems underlying the nicotine antagonist-induced cognitive improvement are still not well understood. There is evidence pointing to the importance of mediodorsal thalamic nucleus, which has direct connections with the frontal cortex. In an earlier set of studies we found that administration of the $\alpha 4\beta 2$ antagonist DH β E directly into the mediodorsal thalamic nucleus either acutely or chronically significantly improved working memory function (Cannady et al., 2009). This contrasts with acute and chronic DH β E-induced memory impairment with infusion in the ventral hippocampus (Arthur and Levin, 2002; Levin et al., 2002).

The current study shows that nicotinic $\alpha 7$ and $\alpha 4\beta 2$ antagonist treatment can significantly improve attentional function. This, together with previous results, provide good evidence that decreasing nicotinic receptor activation can improve cognitive function. Given the complex neural circuits in which nicotinic receptors participate in the neural bases of cognitive function, it is not surprising that in some cases nicotinic receptor activation as well as inactivation can provide therapeutic effects with regard to cognition. Drug development for effective nicotinic treatments for cognitive impairments should not ignore the possible benefit of nicotinic receptor antagonists and desensitizing agents.

Acknowledgments

Supported by NIDA grant DA027990.

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Nicotine-DH β E Interactions Percent Correct

Figure 1.
Nicotine interactions with the nicotinic $\alpha 4\beta 2$ antagonist DH β E, percent correct (mean $\pm$ S.E.M.). N=11

Nicotine Interactions with the DH β E Therapeutic Effect

Figure 2. DH β E reversed the dizocilpine-induced percent correct impairment and nicotine blocked this effect (mean $\pm$ S.E.M.). N=11

MLA Attenuation of Dizocilpine-Induced Attentional Impairment

Figure 3.

The nicotinic $\alpha 7$ antagonist MLA attenuated the dizocilpine-induced percent correct impairment (mean $\pm$ S.E.M.). N=12

Nicotine Interactions with the MLA Therapeutic Effect

Figure 4.

Nicotine does not block the MLA-induced reversal of the dizocilpine-induced percent correct impairment (mean± S.E.M.). N=12

MLA and Nicotine Interactions with Dizocilpine Percent Hit

Figure 5.

Nicotine plus dizocilpine impairs percent hit accuracy, while MLA co-administration reverses this effect (mean $\pm$ S.E.M.). N=12

MLA and Nicotine Interactions with Dizocilpine Percent Correct Rejection

Figure 6.

Dizocilpine impairs percent correct rejection accuracy, an effect that is attenuated by nicotine or MLA (mean $\pm$ S.E.M.). N=12

Table 1

Nicotinic Antagonist Effects on Percent Correct Accuracy

	Dose mg/kg				
	0	1 ^d	2 ^c	4 ^b	8 ^a
DHβ E	81.6±2.6	87.2±1.8	85.8±2.0	85.6±2.0	84.8±1.9
MLA	88.2±1.3	87.3±2.2	87.5±1.3	87.4±1.5	86.0±1.6

Difference from 0 mg/kg:

- ^a =P<0.025,
- ^b =P<0.01,
- ^c =P<0.005,
- ^d =P<0.0005