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

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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 α4β2 receptor antagonist dihydro-β-erythroidine (DHβE) and the α7 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 α4β2 antagonist DHβE 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 α4β2 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.

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 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, 2001; Newhouse et al., 1997). 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 α4β2 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, 2012a). However, sazetidine-A also has an agonist effect at one of the configurations of α4β2 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 α4β2 nicotinic antagonist would have a similar effect for reversing dizocilpine-induced attentional impairments.

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It was hypothesized that the α4β2 nicotinic receptor antagonist, dihydro-β-erythroidine (DHβE), would attenuate attentional impairments caused by dizocilpine.

The effects of the α7 antagonist methyllycaconitine (MLA) were also assessed to compare with the effects of α4β2 blockade and to determine whether previous findings that α7 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 α7 receptors caused by these agonists providing net antagonist effects. Recently, Hahn et al. (2011) found that low doses of MLA effectively improve attentional function of rats. The interactions of both antagonists with nicotine were assessed to determine the interactions of the antagonists with nicotine, which both activates and desensitizes both α7 and α4β2 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 ± 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 DHβE and the other for testing of MLA. In DHβE study rats ($N=11$) were first tested for the acute dose-effect function of DHβE (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 DHβE (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 mg/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. DHβE, MLA, nicotine and dizocilpine were purchased from Sigma (St. Louis, MO, USA). All doses 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 chamber was equipped with a signal light, a house light, two retractable levers, a food cup (Coulbourn Instruments, Lehigh Valley, PA, USA) and a white noise generator (Med Associates Inc., Georgia, VT, USA). 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 lx above a background illumination of 1.2 lx (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) × 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 DHβE 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).