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# Time-dependent effects of nicotine on reversal of dizocilpine-induced attentional impairment in female rats

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

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

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ABSTRACT

Nicotine and nicotinic compounds have been found to attenuate the attentional impairments caused by the glutamate NMDA antagonist dizocilpine (MK-801). The timing of the nicotine effect on attention in rodents has not yet been determined. In the current study, we tested the interaction of dizocilpine with nicotine. Nicotine was given at a range of times (30 to 240 min) prior to dizocilpine administration and before testing on an operant signal detection task. Each rat was assessed with each dose timing. This protocol was repeated twice with one week between phases of testing. In the first phase, correct rejection performance was significantly impaired by 0.05 mg/kg of dizocilpine and this impairment was significantly attenuated by nicotine given sc 30–150 min prior to dizocilpine administration. The greater dizocilpine-induced percent correct rejection impairment seen during the first phase of drug challenge, was significantly attenuated by nicotine given 30 or 90 min before the start of the 1-h test session. During the second phase, the dizocilpine-induced repeated acquisition impairment was more modest. During this phase of testing nicotine administered 60, 90 or 150 min before testing significantly attenuated the dizocilpine-induced impairment. In both phases of testing, nicotine administration 240 min prior to testing was not seen to attenuate the dizocilpine-induced impairment. During the first phase but not the second phase, dizocilpine administration caused a significant impairment in percent hit. Nicotine was not found to have a significant effect in the second phase. Response omissions were significantly increased by dizocilpine during the first, but not the second phase. Nicotine was not found to have any significant effects on response omission. Overall, our data show that nicotine administration prior to dizocilpine administration was able to significantly improve dizocilpine-induced attentional impairment in a time-dependent manner.

## 1. Introduction

Nicotine itself and nicotinic compounds have been shown in many studies to improve cognitive functions such as attention, learning and memory in a variety of species (Alhowail, 2021; Levin et al., 2006; Mirza and Stolerman, 1998; Nespor and Tizabi, 2008; Rezvani et al., 2008, 2010, 2011, 2012; Rezvani and Levin, 2001; Valentine and Sofuoglu, 2018). Both experimental animal and clinical studies support the role of central nicotinic systems in attention, cognition as well as learning and memory (Allison and Shoaib, 2012; Newhouse et al., 2012; Conners et al., 1996). We have shown that nicotine itself and sazetidine-A, a nicotinic partial agonist and α4β2 receptor desensitizing compound, significantly improved dizocilpine-induced attentional impairment in rats (Rezvani et al., 2011; Rezvani et al., 2013). Nicotinic cholinergic systems in the brain have been implicated in the manifestation of several mental disorders such as schizophrenia, Alzheimer's disease, and attention-deficit/hyperactivity disorder (ADHD) (Alhowail, 2021; Conners et al., 1996; Levin et al., 1996; Sahakian et al., 1989; Rezvani and Levin, 2001; Rezvani et al., 2011, 2013; White and Levin, 1999).

The timing of nicotinic effects on cognitive functions is important both for the application of nicotinic therapeutics to reverse or improve cognitive impairment and for learning more about the critical mechanisms of nicotinic effects on improving cognitive functions. However, the timing of nicotine's effect on cognitive functions has not been much studied. Interestingly, in rats we found that the nicotinic α4β2 agonist RJR 2403 caused memory improvement at both one and six hours after administration (Levin and Christopher, 2002). This suggests that it may not be the immediate nicotinic receptor agonist effects that are key for nicotine effects on cognitive function, but either persisting nicotinic receptor desensitization or consequent trans-synaptic circuit-based effects.

Dizocilpine is a noncompetitive antagonist of the *N*-Methyl-D-

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 104790, Durham, NC 21170, USA.
*E-mail address:* azadi@duke.edu (A.H. Rezvani).

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aspartate (NMDA) receptor, a glutamate receptor. Dizocilpine has been shown to disrupt cognitive functions and impairs the acquisition of difficult tasks in rats (Murray et al., 1995; Rezvani et al., 2008) and monkeys (Harder et al., 1998). It has also been used to model symptoms of schizophrenia (Cadinu et al., 2018; Neill et al., 2014). We have shown previously that dizocilpine given systemically significantly impairs sustained attention in rats (Levin et al., 2011), which can be reversed by nicotine and nicotinic agonists (Rezvani et al., 2008, 2011, 2012, Levin et al., 2011). We have previously found a dose of 0.05 mg/kg of nicotine can attenuate the attentional impairment caused by dizocilpine on this attentional test when nicotine was administered 20 min before the start of the test session (Rezvani et al., 2008). We conducted this current study to determine how long the interval between dosing and testing could be extended over which nicotine would still be effective. In the current study, we characterized the time effect function of nicotine on improving dizocilpine-induced attention impairment in adult female rats. We hypothesize that nicotine administration will improve dizocilpine-induced attentional impairment but the magnitude of its effect will be different depending on the time of nicotine administration.

## 2. Materials and methods

### 2.1. Subjects

Adult female Sprague-Dawley rats (Taconic Farms, Germantown, NY, USA) were used in these experiments (N = 15). Rats were housed in groups of three in plastic cages with wood shavings in a vivarium with 12 L: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 ± sem). The treatment and care of the animals were carried out under an approved protocol of the Animal Care and Use Committee of Duke University in an AAALAC-approved facility.

### 2.2. Drug preparation

All drugs were prepared in sterile saline solution. Nicotine ditartrate and dizocilpine maleate were purchased from Sigma-Aldrich (St. Louis, MO, USA). All doses are referred to the salt weights and were injected subcutaneously as 1 ml/kg. The pH of the injected solutions was adjusted to 7.0. All experiments were carried out during the dark phase of the dark-light cycle. All animals in the study received all treatments.

### 2.3. Experimental protocol

The adult female rats (N = 15) were trained on the operant visual signal detection test (Bushnell et al., 1997; Bushnell, 1998). After acquisition of stable baseline performance they were administered (sc) 0.05 mg/kg nicotine and dizocilpine (0.05 mg/kg) with the dose and time combinations given in a repeated measures counterbalanced order. We have previously used the repeated measures counterbalanced design for assessing nicotine interactions with dizocilpine and other drugs on this attentional test and successfully detected nicotine attenuation of impairments (Rezvani et al., 2008). The repeated measures counterbalanced design provides a way for efficiently testing drug effects without conflating dose condition with order of administration. The vehicle saline was used for control injections. At least two days elapsed between consecutive injections. To determine if tolerance developed, the same procedure with all of the dose combinations was repeated starting one week later as Phase 2 with a one-week interval between Phase 1 and Phase 2.

### 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 (Bushnell, 1998).

Rats were trained to perform a visual signal detection task (Bushnell et al., 1997; Bushnell, 1998; Rezvani et al., 2008; Rezvani and Levin, 2003). Animals were tested every day except weekends and holidays. The task was conducted in daily 240-trial sessions approximately 45–60 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, and 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 lever 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 led 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 $p < 0.05$ (two-tailed).

### 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 0.05 mg/kg) and nicotine (vehicle control and nicotine injected 30, 60, 90, 150 and 240 min. Before the start of the session. The percent correct data (percent hit and percent correct rejection), response latency and the number of non-response trials were the dependent measures. Comparisons were made to the vehicle control condition. The effects of nicotine + dizocilpine were evaluated vs. the effects of dizocilpine without nicotine. 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).

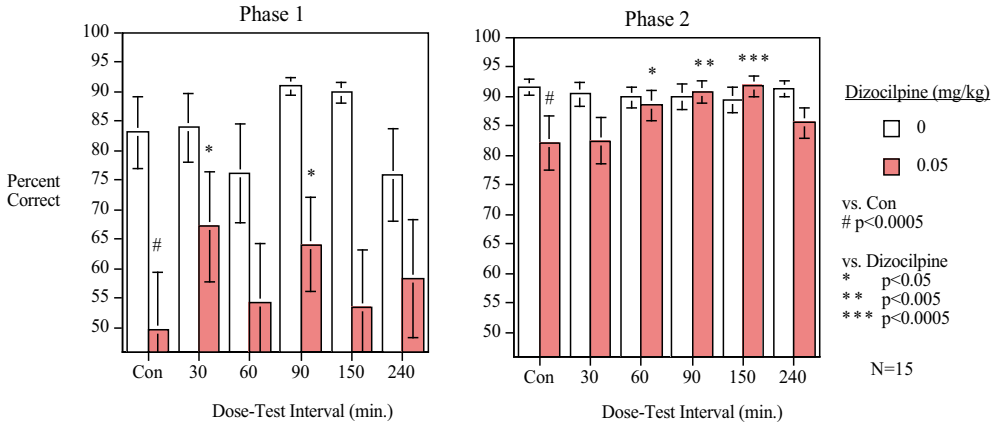


**Fig. 1.** Operant signal detection attention task, Percent correct rejection (mean ± sem) N = 15, Phase 1 was the first time the dose combinations were administered in a counterbalanced order and after a week interval Phase 2 was the second time the doses were given. The nicotine dose was 0.05 mg/kg (sc) and the dizocilpine dose was 0.05 mg/kg (sc).

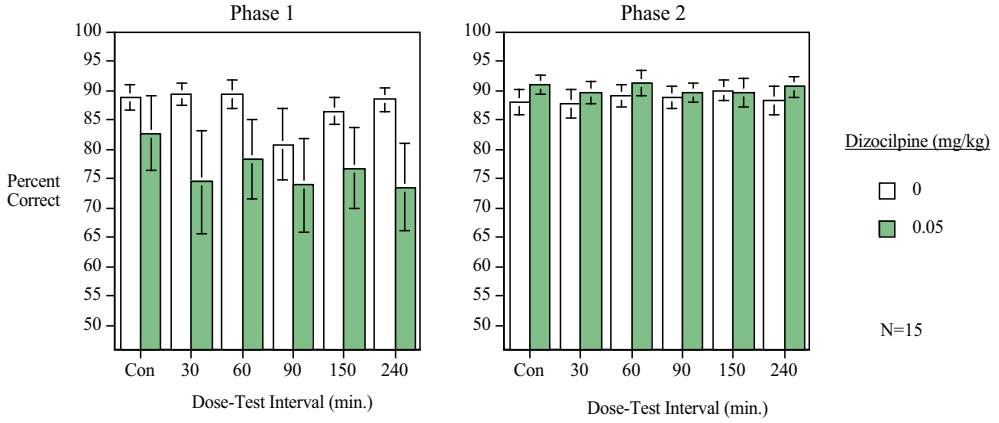


**Fig. 2.** Operant signal detection attention task, Percent hit (mean ± sem) N = 15, Phase 1 was the first time the dose combinations were administered in a counterbalanced order and after a week interval Phase 2 was the second time the doses were given. The nicotine dose was 0.05 mg/kg (sc) and the dizocilpine dose was 0.05 mg/kg (sc).

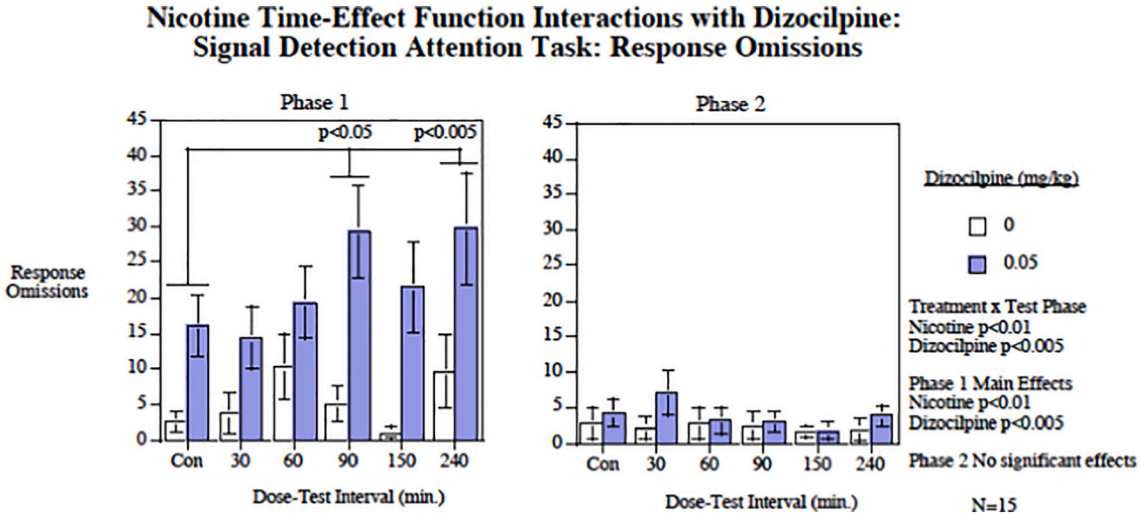


**Fig. 3.** Operant signal detection attention task, Response omissions (mean ± sem) N = 15, Phase 1 was the first time the dose combinations were administered in a counterbalanced order and after a week interval Phase 2 was the second time the doses were given. The nicotine dose was 0.05 mg/kg (sc) and the dizocilpine dose was 0.05 mg/kg (sc).

## 3. Results

The overall analysis of the timing of nicotine interactions with dizocilpine across dosing intervals and test phase showed that there were significant main effects of dizocilpine ($F(1,14) = 30.34$, $p < 0.0005$) and test phase $F(1,14) = 51.00$, $p < 0.0005$) as well as a significant dizocilpine × test phase interaction ($F(1,14) = 37.43$, $p < 0.0005$). Dizocilpine significantly impaired correct rejection in both the first and second test phases but the effect was more prominent in Phase one of the study (Fig. 1). With regard to nicotine time × trial type there was an interaction ($F(5,70) = 2.09$, $p < 0.08$) that prompted follow-up analyses for percent correct rejection and percent hit at each of the doing intervals.

With correct rejection there was an interaction of nicotine timing × dizocilpine × test phase ($F(5,70) = 2.21$ $p = 0.06$). Further analysis showed that nicotine reversal of dizocilpine-induced impairments was differentially present across the timing of nicotine treatment and the phase of testing. As shown in Fig. 1, dizocilpine caused significant impairments in correct rejection during both phases ($p < 0.0005$), but the dizocilpine-induced impairment was much more modest during phase 2. Nicotine treatment significantly attenuated the dizocilpine-induced impairment in both phases, but the timing of the improvement was different in phase 1 and phase 2. In phase 1, nicotine significantly attenuated the dizocilpine-induced impairment at the 30 ($p < 0.05$) and 90 min. ($p < 0.05$) injection-testing intervals. In phase 2 no nicotine-induced improvement was seen at the 30 min. Interval but nicotine did cause significant improvements during the 60 ($p < 0.05$), 90 ($p < 0.005$) and 150 min. Intervals ($p < 0.0005$). By the 240 min. Interval, the nicotine-induced improvement was no longer seen (Fig. 2). So, the beneficial effects of nicotine in reducing dizocilpine-induced impairments in correct rejection was earlier during the phase 1 when the dizocilpine-induced impairment was greater and delayed during phase 2 when the dizocilpine-induced impairment was more modest. The attenuation of the greater dizocilpine-induced impairment during Phase 1 was partial, whereas the reversal of the more modest dizocilpine-induced impairment during Phase 2 was complete.

With percent hit there were no significant main effects but there was an interaction of dizocilpine × phase ($F(1,14) = 4.37$, $p < 0.06$) that led to tests of the simple main effects of dizocilpine in each phase. Dizocilpine effects on percent hit at each phase were not significant (Fig. 2). Neither were there any significant nicotine effects on percent hit in each phase of testing.

With response omissions (Fig. 3) there were significant main effects of dizocilpine ($F(1,14) = 15.20$, $p < 0.005$), nicotine ($F(5,70) = 2.71$, $p < 0.05$) and test phase ($F(1,14) = 18.30$, $p < 0.001$). There were also interactions of dizocilpine × test phase ($F(1,14) = 16.55$, $p < 0.005$) and nicotine × test phase ($F(5,70) = 3.40$, $p < 0.01$) that prompted further analysis of the simple main effects in the first and second phase. In phase 1, there were significant main effects of dizocilpine ($F(1,14) = 16.72$, $p < 0.005$) and nicotine ($F(5,70) = 3.33$, $p < 0.01$). Dizocilpine caused a significant increase in response omissions as did nicotine at the 90 ($p < 0.05$) and 240 min ($p < 0.005$) delays. In phase 2, there were no significant effects of either dizocilpine or nicotine on response omission (Fig. 3).

## 4. Discussion

Our data show that subcutaneous administration of dizocilpine 30 min before testing significantly impaired sustained attention in adult female rats. Dizocilpine-induced impairments were seen in percent correct rejection and response omissions. In these studies, the clearest effect was the development of tolerance to dizocilpine-induced impairments. When compared with the Phase 1 of the experiment, the attenuating effect of dizocilpine was significantly less suggesting development of tolerance to the impairing effect of dizocilpine on sustained attention. Subcutaneous nicotine administration prior to dizocilpine administration significantly improved dizocilpine-induced attentional impairment. Nicotine was effective in attenuating the dizocilpine-induced impairment by significantly increasing the percent correct rejection. This effect was differentially expressed over the time intervals during the first and second treatment phases. Interestingly, the timing of the beneficial effect of nicotine was delayed during Phase 2 compared with Phase 1. The effect of nicotine was selective to correct rejections. Nicotine did not show a significant effect on percent hit or response omission. In the current study, we tested the duration of nicotine's effects on attentional function, specifically how long nicotine effects significantly attenuated the attentional impairments on choice accuracy on the operant visual signal detection task. Nicotine was given at different time points prior to the administration of dizocilpine. Our data show that nicotine was effective in reducing dizocilpine-induced impairment in sustain attention when given up to 90 min prior to dizocilpine in phase 1 and up to 150 min in phase 2. Our data suggest that nicotine-induced reversal of dizocilpine-induced attentional impairments was limited by the development of tolerance to dizocilpine from phase 1 to the repeated challenge in phase 2.

Although we administered nicotine at different time points (from 30 to 240 min prior to dizocilpine injection), pharmacokinetics of nicotine shows that nicotine metabolites stay in the system for relatively a long time. It has been shown that plasma nicotine half-life in rats ranges from 0.9 to 1.1 h in rats. In addition, it has been shown that mean half-lives of urinary excretion of cotinine, cotinine-N-oxide, and allohydroxydemethylcotinine in rats ranges from 4.8 to 5.3 h, from 7.9 to 8.2 h, and from 9.9 to 11.0 h, respectively (Kyerematen et al., 1988). It is possible that the effect of nicotine on sustained attention depends on the levels of its metabolites at different time points. In addition, the magnitude of the effects might depend on the magnitude of the attentional impairment. The different effects of nicotine at different time points on improving sustained attention and probably other cognitive behaviors is an interesting concept that needs to be further investigated.

In addition to its addiction liability, nicotine is involved in many neuronal systems including learning and memory as well as attention. Nicotinic systems in the brain also have been shown to be involved in some mental diseases such as attention deficit disorder (Conners et al., 1996) as well as schizophrenia with nicotine having effects of attenuating cognitive deficits (Alhowail, 2021; Levin et al., 2006; Sahakian et al., 1989; White and Levin, 1999). Nicotine skin patch and a variety of nicotinic agonists have shown to improve cognitive performance (Alhowail, 2021; White and Levin, 1999). Previously, we have found that nicotine can attenuate dizocilpine-induced cognitive impairments including deficits in working memory on the radial-arm maze and deficits in the signal detection task as used in the current study (Rezvani et al., 2008; Rezvani and Levin, 2003).

Overall, this study showed that nicotine given at different points prior to dizocilpine treatment could significantly improve dizocilpine-induced impairment in sustained attention. However, the improving effect of nicotine was time dependent. These findings are in agreement with some clinical studies demonstrating nicotine-induced attentional improvements in several mental cognitive disorders such as Alzheimer's disease (Sahakian et al., 1989; Majdi et al., 2018; White and Levin, 1999, 2004), mild cognitive impairment (Newhouse et al., 2012; White and Levin, 2004) and attention deficit hyperactivity disorder (ADHD) (Conners et al., 1996; Levin et al., 1996). Nicotinic compounds with more selective effects may even be more effective in improving impaired attention. However, the effects may be different at different time points.

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