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Nicotinic–glutamatergic interactions and attentional performance on an operant visual signal detection task in female rats

Amir H. Rezvani[a,*], Edward D. Levin[a,b]

[a] Department of Psychiatry, Duke University Medical Center, 341 Bell Building, Box 3412, Durham, NC 27710, USA
[b] Department of Pharmacology, Duke University Medical Center, Durham, NC 27710, USA

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Abstract

Nicotinic systems have been shown to be critically involved in cognitive function including attention. Nicotine has been shown to improve performance on attentional tasks in humans with Alzheimer's disease, schizophrenia and attention deficit hyperactivity disorder. Nicotine has mixed effects on attentional accuracy in unimpaired rats with findings of increased, reduced or unaltered accuracy under different conditions. Nicotine effects on attentional function in rats might be more clearly seen in reversing impaired performance. The current study determined nicotine effects on attentional accuracy reduced by the NMDA receptor antagonist dizocilpine (MK-801). Sprague–Dawley rats ($N=35$) were trained on a food-motivated two-lever operant task with one lever correct after a brief visual signal (0.027–1.22 lx) for hits and the other lever correct after the absence of a signal for correct rejections. First, a dose response study of dizocilpine was conducted to determine the threshold for impairment. The rats were administered acute doses of dizocilpine (0, 12.5, 25 and 50 μg/kg, sc). The 50 μg/kg dose caused significant ($p<0.0005$) reduction in percent hit at the four highest signal intensities. Percent correct rejection was also significantly lowered by this dose ($p<0.005$). No effect was seen with 12.5 μg/kg and only minimal effect seen with 25 μg/kg. Then, nicotine–dizocilpine interactions were investigated. The rats were administered acute doses of dizocilpine (0, 37.5 and 50 μg/kg, sc) and nicotine (0, 25 and 50 μg/kg, sc), alone or in combination. Percent hit was affected by nicotine and dizocilpine in a complex fashion with only the nicotine × dizocilpine × signal intensity interaction being significant ($p<0.05$). Percent correct rejection showed a more straightforward effect. Percent correct rejection was significantly reduced by 50 μg/kg dizocilpine ($p<0.025$). The addition of 25 μg/kg of nicotine significantly ($p<0.025$) reversed the dizocilpine-induced reduction of correct rejection. This study shows that dizocilpine reduces signal detection accuracy in a dose-dependent fashion. Nicotine can partially counteract an aspect of this reduction by reversing the dizocilpine-induced reduction of correct rejection.

Keywords: Dizocilpine; MK-801; NMDA receptor; Nicotine; Attention; Cognition

1. Introduction

Neuronal nicotinic systems play an important role in memory and attentional functions. In humans, the most prominent effect of the cholinergic agonist nicotine on cognitive function is improved attention (Levin et al., 2001, 1998b, 1996b; Peeke and Peeke, 1984; Warburton and Mancuso, 1998; Warburton et al., 1992). Clinical studies using nicotine via other means than tobacco, such as skin patches and other nicotinic agonists, have demonstrated the efficacy in improving attentional impairments associated with Alzheimer's disease (Lawrence and Sahakian, 1995; Newhouse et al., 1997; Sahakian et al., 1989; White and Levin, 1999), attention deficit hyperactivity disorder (Levin et al., 2001, 1996b; Wilens et al., 1999) and schizophrenia (Levin et al., 1996a).

Nicotinic compounds have been shown to improve attention and reduce distractibility in rodents (Mirza and Bright, 2001; Mirza and Stolerman, 1998; Muir et al., 1995; Rezvani et al., 2002; Stolerman et al., 2000) and nonhuman primate models (Terry et al., 2002) as well. However, nicotine-induced improvement has been more difficult to detect in rodents than in humans. Nicotinic antagonist-induced impairments in attention have been readily documented in the operant signal detection task; however, nicotinic agonist-induced improvements of attention have been more elusive

* Corresponding author. Tel.: +1-919-668-1880; fax: +1-919-681-3416.
E-mail address: Azadi@duke.edu (A.H. Rezvani).

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with some studies finding nicotinic-induced improvements (McGaughy et al., 1999; Rezvani et al., 2002) and others not (Bushnell et al., 1997; Turchi et al., 1995).

It may be the case that nicotinic agonist-induced improvement is most evident in reversing impaired attentional performance. Attention may be difficult to improve in the signal detection task because with extensive training, subjects may already be performing at their best possible levels. Drug-induced attentional impairment may be a useful model for examining nicotine effects because not only do they provide compromised performance against which nicotine may act, but also because the specific receptor actions of those drugs can lend insight into the mechanisms of action of nicotinic treatment. Recently, Terry et al. (2002) found that the nicotinic agonist SIB-1553A significantly improved performance of rats on a five-choice attentional task in rats, but only when accuracy was reduced either with a distracting stimulus or by challenge with the NMDA-sensitive glutamate receptor antagonist dizocilpine (MK-801). In the current study, we sought to determine nicotinic–NMDA interactions in another test of attentional function, the operant visual signal detection task. The operant visual signal detection is a useful technique in which both sensory function and attention can be simultaneously measured (Bushnell et al., 1997). Previously, we have found nicotine-induced improvements on this task in both low and high performing rats, demonstrating that poor performance per se is not a requirement for showing nicotine-induced attentional improvement (Rezvani et al., 2002). Specific interactions of nicotinic systems with other neurotransmitter receptor systems may be important with regard to nicotinic actions on attentional function.

MK-801 is a dissociative anesthetic that, at pharmacologically relevant doses, acts as noncompetitive of the NMDA receptor by binding to a site in the channel (Tsai and Coyle, 2002). There is convincing evidence that hypofunction of NMDA receptors plays a primary role in pathophysiology of schizophrenia (Tsai and Coyle, 2002). The aims of the present study were to determine the role of NMDA–glutamate systems in attentional function using the visual signal detection task and to find out if nicotine can counteract the disruptive effects of MK-801 on attention. First, a dose response function for MK-801 was established. Then, rats were injected with different doses of MK-801 and nicotine and their performance in the visual signal detection task was assessed. We hypothesized that acute nicotine administration will diminish the disruptive action of MK-801 in rats on attention on this task.

2. Materials and methods

2.1. Animals

Adult (70 days old at the beginning of training) female Sprague–Dawley rats ($n = 35$) (Taconic Farms, Germantown, NY, USA) were used. Animals were housed in groups of three in a vivarium with 12L:12D light schedule (light on at 7:00 p.m.). Room temperature was maintained at 21 ± 1 °C and relative humidity controlled at $50\% \pm 10\%$. All training and testing sessions were performed during the dark phase of the circadian cycle, between 9:00 a.m. and 4:00 p.m. Rats were fed once daily after testing such that their body weights were kept at 80–85% of free feeding values. Rats had ad libitum access to water in their home cage. 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 approved facility. These rats had previously been tested for nicotine and mecamylamine response on the signal detection task (Rezvani et al., 2002).

2.2. Experimental protocol

There were two sets of experiments in the current study to characterize the effects of the NMDA receptor antagonist dizocilpine (MK-801) on attentional performance in an operant signal detection task and the interaction of dizocilpine with nicotine. In Exp. 1 the dizocilpine dose effect function was determined. In Exp. 2 nicotine interactions with an effective and a threshold dose of dizocilpine were determined.

2.2.1. Exp. 1: Dizocilpine dose effect function

Animals were injected subcutaneously with saline or one of the three doses of dizocilpine (12.5, 25 and 50 μ/kg) and 10 min later were transferred in operant boxes for testing. The interval between different doses of dizocilpine was 2–4 days. All rats received all treatments following a counterbalanced design.

2.2.2. Exp. 2: Nicotine interactions with dizocilpine

To determine nicotine interactions with dizocilpine, we studied nicotine dose effect functions with two dizocilpine doses, one high clearly suprathreshold for causing impairment (50 μg/kg) and one lower near the threshold dose for causing impairment (37.5 μg/kg). The high dizocilpine dose from Exp. 1 (0 or 50 μg/kg) and nicotine (0, 25 or 50 μg/kg) were administered alone or together. To study the interaction between a threshold dose of dizocilpine and nicotine, the rats were injected with 0 or 37.5 μg/kg dizocilpine and nicotine (0, 12.5, 25 and 50 μg/kg), alone or together. The 12.5 μg/kg nicotine dose was only run with the lower dizocilpine and did not have any interactive effect. Because it was not run also with the higher dizocilpine dose, it was not included in the overall analysis of the dizocilpine–nicotine interactions. The rats began testing 10 min after drug injection. All rats received all treatments following a counterbalanced design. The interval between different treatments was 2–4 days.

2.3. Drug preparation and dosing

Both nicotine ditartrate and dizocilpine HCl (MK-801) (Sigma, St. Louis, MO, USA) were prepared in 0.09% saline solution. Both drugs were injected subcutaneously 10 min before testing in a volume of 2 ml/kg body weight in a counterbalanced order within each experiment. There was at least a 2 day-interval between experiments. All doses of nicotine and dizocilpine were calculated as the weight of the salt.

2.4. Visual signal detection task

The operant chambers 29 × 25 × 29 cm (HWD) were equipped with a signal light, a house light, two retractable levers, 13 cm apart, 2.5 cm above the floor of the chamber inserted 2.5 cm horizontally into the chamber, a food cup in the center of the front panel of the chamber, 2.2 cm above the floor (Coulbourn Instruments, Lehigh Valley, PA, USA), and a white noise amplifier mounted above the signal lever generating background white noise of about 65 dB (Med Associates, Georgia, VT, USA). During training the signal or cue light was located above the designated lever and as the rats advanced in learning the task the signal light was moved to 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 1–7 (0.027, 0.073, 0.148, 0.269, 0.466, 0.762 and 1.22 lx) above a background illumination of 1.2 lx. Signals were generated using Med Associates software running a Pentium computer processor using the Windows operating system. The same software controlled all aspects of the behavioral testing.

Rats were trained to perform a visual signal detection task (Bushnell, 1998; Bushnell et al., 1997). The task, illustrated in Fig. 1, was conducted in daily 300-trial sessions, divided into three 100-trial blocks, each block approximately 20 min in duration. Two trial types, "signal" and "blank", were presented in equal number in each session, in groups of four (two signal and two blank, in random order) at each signal intensity. Each signal trial included a pre-signal interval, the signal (cue light) and a post-signal interval. The pre-signal intervals were selected randomly from 12 different values ranging from 0.3 to 24.4 s. Following the signal, a post-signal interval of 2, 3 or 4 s (selected randomly) occurred. These temporal parameters yield a trial presentation rate of five trials per minute. Blank trials were presented identically, except the signal light was not present. For half the rats, the left lever was defined as the signal lever and the right lever as the blank lever; the opposite assignment was made for the remaining rats.

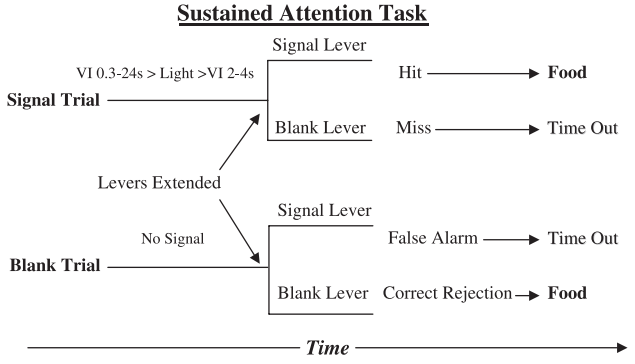

Fig. 1. Signal detection task sequence of trials. This task comprised two types of trials, signal and blank, which differed only in that a signal was presented in each signal trial and omitted in blank trials. In each trial, the rat pressed either of two retractable levers to report that a signal had or had not occurred in that trial. Four possible outcomes result: hit, miss, false alarm and correct rejection. Hits and correct rejections were followed by delivery of food; misses and false alarms by a 2-s "time out" period without food. VI stands for variable intervals for pre- and post-signal during the signal trial.

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 when one was pressed or if 5 s passed without a press. If no press occurred, a response failure was recorded and the trial was not repeated. Every correct response (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 total darkness (time out) (Bushnell et al., 1997).

2.5. Behavioral measures and statistical analysis

Following dependent variables were recorded for each signal intensity across the three blocks of trials in each session: hits (signal-level presses on signal trials), correct rejections (blank-lever presses on blank trials), misses (blank-lever presses on signal trials) and false alarm (signal-lever presses on blank trials).

The analysis of percent hit also included signal light intensity as a within-subjects factor. The test session was divided into three blocks of 100 trials and measures of response accuracy were analyzed across blocks as a repeated measure. The threshold for significance was $p < 0.05$. The Huynh–Feldt correction was used to correct for non-sphericity of variance across the repeated measures. The Superanova/Statview computer program (SAS, Cary, NC) was used for the statistical analysis. Planned comparisons were made to test for non-additivity of nicotine and dizocilpine effects. Significant interactions were followed up by tests of the simple main effects.

3. Results

3.1. Exp. 1: Dizocilpine dose effect function

Compared with control saline, dizocilpine at the high dose of 50 μg/kg caused a significant impairment in percent hit response except at lowest intensity in which it caused a

significant increase in percent hit. There was a significant dizocilpine × session time block interaction ($F(6,168) = 4.13$, $p < 0.005$). As shown in Fig. 2, follow-up tests of the simple main effects demonstrated that there were significant reductions in percent hit caused by the 50 μg/kg dizocilpine dose relative to control injections during the middle ($p < 0.001$) and late ($p < 0.0005$) time blocks of the session.

There was also a significant dizocilpine × signal intensity interaction ($F(18,504) = 5.39$, $p < 0.0001$). As shown in Fig. 3, the 50 μg/kg dizocilpine dose caused significant ($p < 0.0005$) reductions in percent hit relative to control injections for levels 4–7 of signal intensities. At level 3 of signal intensity, the 25 μg/kg dizocilpine dose caused a significant ($p < 0.05$) reduction in percent hit relative to control. With the lowest signal intensity, the 50 μg/kg dizocilpine dose caused a significant increase in percent hit ($p < 0.01$). The three-way interaction of dizocilpine × session time block × signal intensity was also significant ($F(36,1008) = 1.50$, $p < 0.05$). As shown in Fig. 4, at the levels 4–7 of signal intensities, the 50 μg/kg dizocilpine dose caused significant ($p < 0.005$) reduction in hit percent relative to control vehicle during the middle and late parts of the session. No effect was detected at these signal intensities during the initial part of the session. At the two lowest signal intensities during the middle portion of the session, significant dizocilpine-induced increases in hit percent were seen. The 50 μg/kg dizocilpine dose significantly ($p < 0.05$) increased percent hit at the lowest signal intensity during the middle portion of the test. The 12.5 μg/kg dizocilpine dose significantly ($p < 0.05$) increased percent hit at the level 2 of signal intensity during the middle portion of the test. Interestingly, at the level 3 of signal intensity, the 50 μg/kg dizocilpine dose significantly ($p < 0.05$) increased percent hit in the first session block and significantly ($p < 0.05$) reduced percent hit in the last session block. This alteration in the valence of the dizocilpine effect relative to control was mainly due to the great change in performance from the first to the third session block. In the first session block with control injections the rats had 35.7 ± 4.6 (mean ± S.E.M.) percent hit while with 50 μg/kg dizocilpine they had 45.0 ± 4.4 percent hit. In contrast, in the third session block the rats had 61.1 ± 3.5 percent hit, while with 50 μg/kg dizocilpine they had 50.3 ± 6.3 percent hit. In all cases, significant dizocilpine effects were consistently in the direction of random responding (50%).

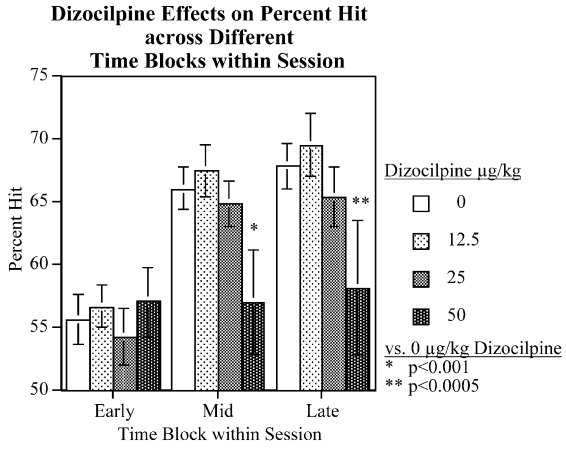

Fig. 2. Effects of different doses of dizocilpine on percent hit (mean ± S.E.M.) during the early, mid and late parts of the test session. $N = 35$.

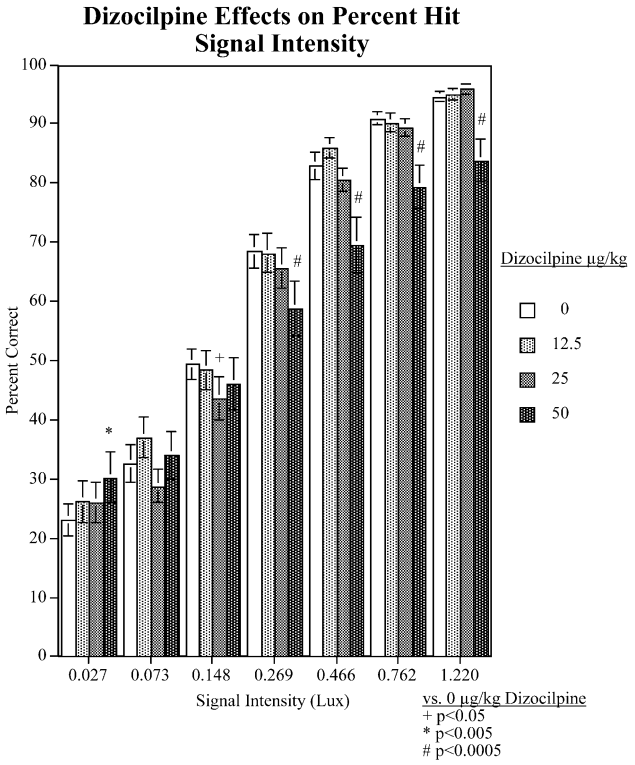

Fig. 3. Effects of different doses of dizocilpine on percent hit (mean ± S.E.M.) over the range of different signal intensities. $N = 35$.

Percent correct rejection was significantly lowered by the high dose of dizocilpine (Fig. 5). The main effect of dizocilpine treatment was significant ($F(3,84) = 8.88$, $p < 0.005$). Comparisons of the different dizocilpine doses vs. control showed that the 50 μg/kg dose significantly ($p < 0.005$) lowered percent correct rejection from 85.6 ± 2.0% after control treatment to 75.3 ± 3.8% after 50 μg/kg dizocilpine. There was also a significant dizocilpine × session time block interaction ($F(6,168) = 5.50$, $p < 0.005$). As shown in Fig. 5, there were significant reductions in percent correct rejection with 50 μg/kg dizocilpine relative to control in each session block, but the effect was smaller in the first session block ($p < 0.05$) than in the second and third blocks ($p < 0.0005$). Unlike with percent hit control performance did not appear to change over blocks within the session.

Response latency was significantly ($F(3,96) = 4.48$, $p < 0.001$) increased by dizocilpine (Fig. 6). Across the dose range tested, there was a significant increase in latency ($p < 0.025$) with the highest dose of 50 μg/kg dizocilpine

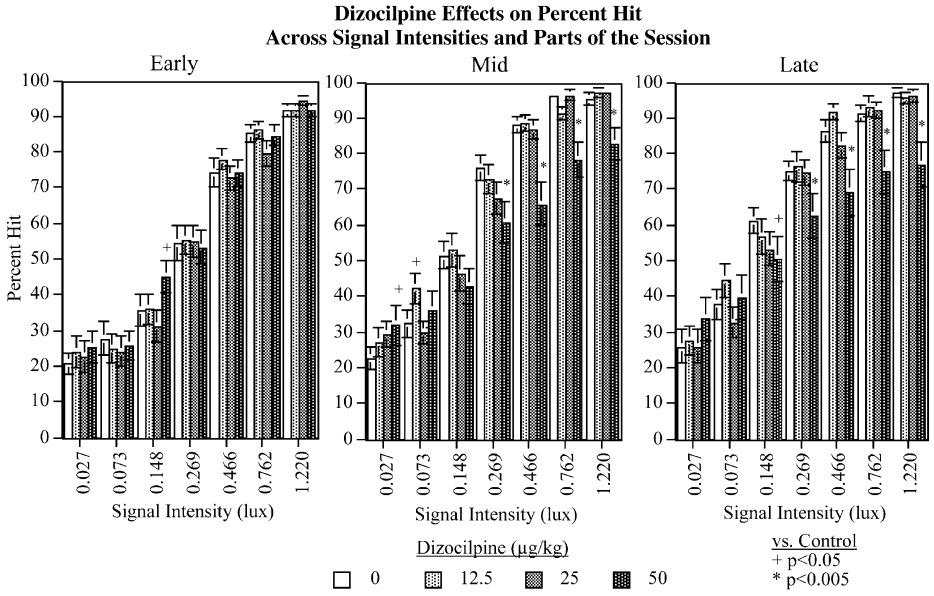

Fig. 4. Effects of different doses of dizocilpine on percent hit (mean ± S.E.M.) during the early, mid and late parts of the test session and the range of different signal intensities. $N = 35$.

compared with control. Neither of the lower doses significantly affected response latency.

Dizocilpine caused a significant increase in the number of nonresponse trials ($F(3,99) = 33.15$, $p < 0.0001$). As with latency, it was only the highest dizocilpine dose (50 μg/kg) that caused a significant increase in nonresponse trials ($p < 0.0001$). With saline the rats averaged 1.0 ± 0.6 nonresponse trials/session, with 12.5 μg/kg dizocilpine they averaged 1.4 ± 0.5, with 25 μg/kg 3.4 ± 1.7, and with 50 μg/kg 30.3 ± 4.4.

3.2. Exp. 2: Nicotine interactions with dizocilpine

Percent hit was significantly affected by nicotine and dizocilpine in a complex fashion. The three-way interaction of nicotine × dizocilpine × signal intensity was significant ($F(24,480) = 1.83$, $p < 0.05$). Fig. 7 shows the differential effects of nicotine and dizocilpine across the signal intensity range. Tests of the simple main effects at the individual signal intensities showed that without dizocilpine, 50 μg/kg nicotine significantly ($p < 0.025$) increased percent hit relative to control at the lowest signal intensity. No differential effect of nicotine across time blocks was detected. At the level 7 of signal intensity ($p < 0.025$) and the level 6 of signal intensity, 50 μg/kg nicotine significantly ($p < 0.005$) decreased percent hit relative to control. With 37.5 or 50 μg/kg dizocilpine co-administration, significant nicotine-induced percent hit increase at the low signal intensity and percent hit decrease at high intensities were no longer seen. Rather, there were occasions of significant nicotine-induced reductions in percent hit in the lower range of signal intensities. With 37.5 μg/kg dizocilpine, 50 μg/kg nicotine significantly ($p < 0.05$) reduced percent hit relative to con-

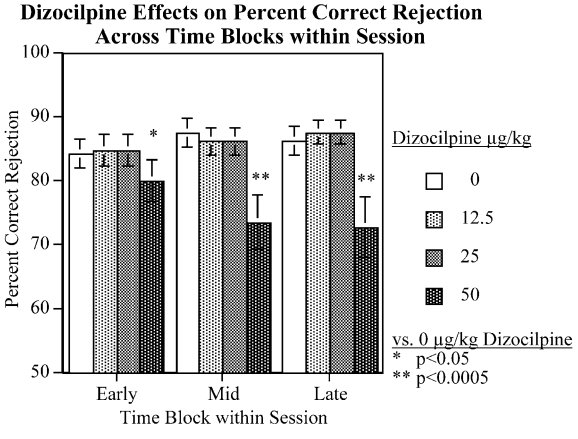

Fig. 5. Effects of different doses of dizocilpine on percent correct rejection (mean ± S.E.M.) during the early, mid and late parts of the test session. $N = 35$.

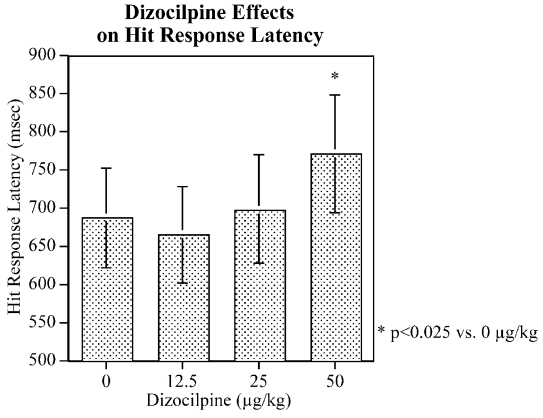

Fig. 6. Effects of different doses of dizocilpine on hit response latency (mean ± S.E.M.). $N = 35$.

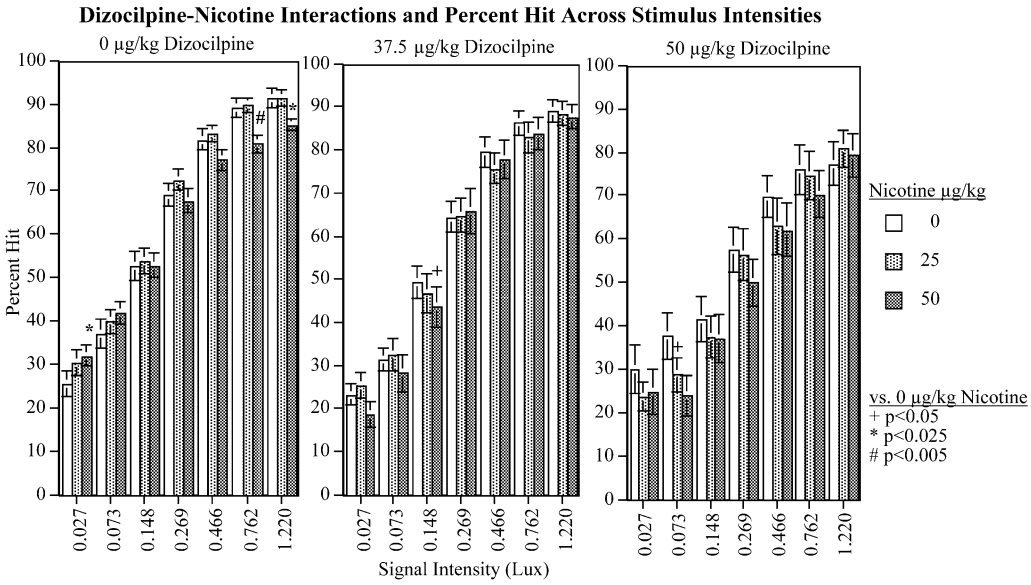

Fig. 7. Dizocilpine interactions with nicotine, percent hit (mean ± S.E.M.) across the range of signal intensities. $N = 35$.

trol at the level 3 of signal intensity. With 50 µg/kg dizocilpine, 25 µg/kg nicotine significantly ($p < 0.05$) reduced percent hit relative to control at the level 2 of signal intensity.

Percent correct rejection was affected by nicotine and dizocilpine in a much more straightforward fashion (Fig. 8). Percent correct rejection was reduced by 50 µg/kg dizocilpine ($p < 0.025$) compared to control injections. The addition of 25 µg/kg of nicotine to 50 µg/kg dizocilpine significantly ($p < 0.025$) blocked this attenuating effect of dizocilpine on correct rejection.

Response latency was significantly lengthened by dizocilpine ($F(2,60) = 5.28$, $p < 0.01$) from an average of 637 ± 55 ms without dizocilpine to an average of 804 ± 84 ms with 50 µg/kg dizocilpine for a significant slowing of response with the higher dose ($p < 0.01$). The lower dose of dizocilpine did not cause a significant slowing of response.

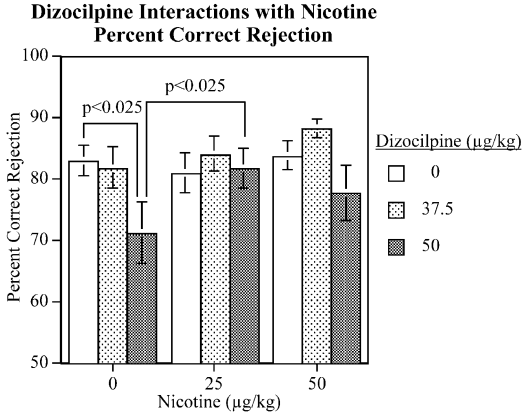

Fig. 8. Dizocilpine interactions with nicotine, percent correct rejection (mean ± S.E.M.). $N = 35$.

There was no significant effect of nicotine or nicotine × dizocilpine interaction.

The incidence of nonresponse trials was significantly increased by dizocilpine ($F(2,60) = 27.49$, $p < 0.0001$). With saline the rats averaged 1.3 ± 0.4 response omissions and with 50 µg/kg of dizocilpine they averaged 18.0 ± 3.4 for a significant increase with the higher dose ($p < 0.0001$). The lower dose of dizocilpine did not cause a significant effect. Nicotine did not have an effect of its own or significantly influence the dizocilpine effect.

4. Discussion

This study demonstrated that NMDA blockade with dizocilpine effectively impaired sustained attention as measured by choice accuracy on this visual signal detection operant task. The dizocilpine-induced deficit was seen both in terms of percent hit and percent correct rejection. Nicotine co-treatment was effective in reversing the dizocilpine-induced correct rejection deficit. This effect was selective to correct rejection as no consistent effect was seen with reversal of dizocilpine-induced deficits in percent hit. Nicotinic-induced glutamate release (McGehee et al., 1995) may be involved in nicotine's reversal of dizocilpine-induced attentional impairment.

Dizocilpine was shown to cause a significant impairment in attentional function by reducing percent hit responses. Only the high dose of 50 µg/kg was effective. The threshold for effect on this measure was between 25 and 50 µg/kg. When the rats were administered 50 µg/kg of dizocilpine, they did not show the improvement in percent hit over the course of the session that was seen with control and lower doses of dizocilpine (12.5 and 25 µg/kg) (Fig. 2). This improvement in percent hit over the course of the

session has previously been seen in this task (Rezvani et al., 2002). However, in the study of Bushnell et al. (1997), the performance of rats in this task was maintained over session blocks. It is possible that rats in the current study had not attained full asymptotic performance levels. The 50 μg/kg dizocilpine dose had the most pronounced impairment in percent hit when the stimulus was bright and clearly differentiable (Fig. 3). This suggests that the dizocilpine effect was not due to visual dysfunction. In that case, one would expect the most pronounced effect with the lower intensity stimuli, which are more difficult to detect. Interestingly, there was a significant increase in percent hit caused by 50 μg/kg of dizocilpine at the lowest intensity. At this barely detectible intensity, the rats responded far more often when there was no stimulus than when there was. The effect of 50 μg/kg may have been one of loss of stimulus control with performance retreating closer to chance (50%) at both the high and low stimulus intensities. The 50 μg/kg dizocilpine dose caused a slight, though significant, increase in hit response latency. It does not appear that the magnitude of this effect (84 ms) would in itself cause the observed choice accuracy impairments. The dizocilpine impairment of percent correct rejection also emerged over the course of the session (Fig. 5), consistent with the effect on percent hit. The fact that the effect of dizocilpine is more pronounced in mid and late blocks of the session may suggest its pharmacokinetic profile in its action.

Nicotine did have significant interactions with dizocilpine. Nicotine (25 μg/kg) significantly reversed the dizocilpine (50 μg/kg)-induced percent correct rejection deficit (Fig. 8). The nicotine interactions with dizocilpine with regard to percent hit performance were more complicated with a significant ($p < 0.05$) three-way interaction of nicotine × dizocilpine × signal intensity (Fig. 7). Nicotine attenuation of dizocilpine-induced percent hit impairment was not seen. The nicotine-induced reversal of dizocilpine-induced impairments on this task appears to be selective to percent correct rejection. The neurobehavioral mechanisms for this selective effect are not entirely clear. This dose range of nicotine has previously been shown on this task to modestly improve correct rejection performance but have no apparent effect on percent hit (Rezvani et al., 2002). Bushnell et al. (1997) have demonstrated that nicotine at a higher dose (0.083 mg/kg) increased percent hit significantly. One difference between hit and correct rejection in this task is that the signal for hit is often near the threshold for sensory discrimination, as evidenced by the less than chance (50%) performance for the lower end to the signal intensity range, whereas correct rejection trials are always the same with no stimulus. The hit measure results from a combination of sensory and attentional function, whereas the correct rejection measure does not have the same component of sensory function. The correct rejection measure may be a clearer measure of attentional performance without variable demand on sensory function.

Nicotine may enhance cognition by direct effects on attention and by interacting with the presynaptic nicotinic acetylcholine receptors to facilitate the release of acetylcholine, dopamine, serotonin, γ-aminobutryic acid, norepinephrine and glutamate (Wonnacott, 1997). The NMDA–glutamate receptor system has been demonstrated to be involved in cognitive function (Wozniak et al., 1990) and there is neuropharmacological evidence that NMDA–glutaminergic and nicotinic systems in the brain are functionally related. Levin et al. (1998a) have shown that nicotine can attenuate the memory impairment caused by the NMDA receptor antagonist dizocilpine (MK-801) in rats. Tizabi et al. (1998) have demonstrated that nicotine and mecamylamine dose-dependently blocked dizocilpine-induced popping in mice. It has been shown that dizocilpine can impair attention. Dai and Carey (1994) found a dose-dependent decrease in animal's response to a stimulus object, suggesting impairment of attention by dizocilpine.

NMDA receptor blockade has been proposed as a model of schizophrenia, inasmuch as this treatment is psychotomimetic. Nicotine's attenuation of dizocilpine-induced attentional impairment in the current study and the recent study of Terry et al. (2002) as well as the nicotine's attenuation of dizocilpine-induced memory impairment (Levin et al., 1998a) may be relevant to reported nicotine-induced cognitive improvement in schizophrenia (Levin et al., 1996a) and for the development of novel nicotinic treatments for schizophrenia-related cognitive impairment.

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