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Effects of Tobacco Smoke Constituents, Anabasine and Anatabine, on Memory and Attention in Female Rats

Edward D. Levin, Ian Hao, Dennis Burke, Marty Cauley, Brandon J. Hall, and Amir H. Rezvani

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

Abstract

Nicotine has been well characterized to improve memory and attention. Nicotine is the primary, but not only neuroactive compound in tobacco. Other tobacco constituents such as anabasine and anatabine also have agonist actions on nicotinic receptors. The current study investigated the effects of anabasine and anatabine on memory and attention. Adult female Sprague-Dawley rats were trained on a win-shift spatial working and reference memory task in the 16-arm radial maze or a visual signal detection operant task to test attention. Acute dose-effect functions of anabasine and anatabine over two orders of magnitude were evaluated for both tasks. In the radial-arm maze memory test, anabasine but not anatabine significantly reduced the memory impairment caused by the NMDA antagonist dizocilpine (MK-801). In the signal detection attentional task, anatabine but not anabasine significantly attenuated the attentional impairment caused by dizocilpine. These studies show that non-nicotine nicotinic agonists in tobacco, similar to nicotine, can significantly improve memory and attentional function. Both anabasine and anatabine produced cognitive improvement, but their effectiveness differed with regard to memory and attention. Follow-up studies with anabasine and anatabine are called to determine their efficacy as therapeutics for memory and attentional dysfunction.

Keywords

Anabasine; Anatabine; Dizocilpine; Attention; Memory; Signal Detection Task; Radial-arm Maze

Introduction

Nicotine, the principal psychoactive chemical in tobacco, has been shown to significantly improve working memory and attention in a variety of preclinical and clinical studies (Rezvani and Levin, 2001). Indeed, previous reports have suggested that the cognitive enhancing effects of nicotine likely contribute to the continuance of tobacco use in some smokers, particularly among individuals with mild cognitive impairment or schizophrenia (Kumari and Postma, 2005; Mihailescu and Drucker-Colin, 2000). Unfortunately the abuse liability associated with nicotine has greatly discouraged its therapeutic usage as anything

more than an aid for quitting tobacco use. However, while nicotine is the primary alkaloid found in tobacco, it is not the only nicotinic acetylcholine receptor (nAChR) agonist present. Among more than 5000 chemical compounds that have been identified in tobacco smoke, there are several other alkaloids with nAChR activity that are present, albeit at much lower levels (Huang and Hsieh, 2007). It is unknown whether these minor nicotinic ligands possess cognitive enhancing properties of their own. Two of these alkaloids that have received increased attention recently are anabasine and anatabine. Anabasine and anatabine are both structurally similar to nicotine, and both compounds are ligands for nAChRs (Daly, 2005; Maciuk et al., 2008; Rodgman, 2009). Each compound can substitute for nicotine in discrimination tasks in rodents and both have been found to significantly affect nicotine self-administration; a low dose of anabasine has been shown to increase nicotine self-administration (Hall et al., 2014), while high doses of both compounds have been shown to decrease nicotine self-administration (Brioni et al., 1994; Caine et al., 2014; Hall et al., 2014). Each alkaloid may serve as a biomarker for tobacco use (Jacob et al., 1999). Between the two compounds, anabasine has been the more studied; much of the research with anabasine has been directed toward the compound's abuse potential (for review, see Hoffman and Evans, 2013). A recent study has shown that anabasine attenuates nicotine withdrawal in rodents (Caine et al., 2014). While anatabine has received somewhat less attention than anabasine, there is growing interest in anatabine for its potential as an anti-inflammatory agent (Lanier et al., 2013; Paris et al., 2013). What is currently unknown is whether these two nicotinic ligands may serve as cognitive enhancers.

Considerable effort has been expended to determine the cognitive enhancing effects of nicotinic drugs. In addition to nicotine itself, a variety of nicotinic drugs including RJR-2403, MEM-3454, ABT-418, AZD-0328, and many others, have been shown to improve memory and attention in preclinical animal models (for review, see Terry et al., 2011). These drugs have typically been agonists designed to target the $\alpha 4\beta 2$ and $\alpha 7$ nAChR subtypes. However, to date there are no published studies examining the potential for either anabasine or anatabine as cognitive enhancing agents. Both compounds are tolerated across a much wider dose range than nicotine in rodents, as observed by a lack of effect on food motivated lever responding except for very high doses (Caine et al., 2014; Hall et al., 2014). Anabasine is a partial agonist at $\alpha 4\beta 2$ nAChRs with lower affinity than nicotine, but it has a greater affinity than nicotine for the $\alpha 7$ subtype, at which it is a full agonist and hypothesized to exert most of its effects *in vivo* (Daly, 2005; Kem et al., 1997). The $\alpha 7$ nAChR subtype has long been thought to play a significant role in learning and memory largely due to its expression in the hippocampus, and has been a valued target for cognitive enhancement (Buccafusco, 2004; Kem, 2000), making anabasine an ideal candidate compound. Less is known about the nicotinic receptor actions of anatabine, but it has been identified as a nAChR ligand through the $\alpha 3\beta 4$ subtype (Maciuk et al., 2008). The current studies were conducted to determine whether anabasine or anatabine would affect memory and attention. It was hypothesized that pretreatment with anabasine or anatabine would significantly improve working and reference memory in the radial arm maze task and also improve attentional processes in the visual signal detection task. It was also hypothesized that treatment with anabasine or anatabine would reverse the memory and attentional impairment in these cognitive tasks produced by pretreatment with the N-Methyl-D-

aspartate (NMDA) antagonist dizocilpine (MK-801). Dizocilpine was selected as a cognitive impairing agent because it reliably causes impairments in both memory in the radial-arm maze (Levin et al., 1998) and attentional function in the visual signal detection task (Rezvani et al., 2009) and is a good model of the cognitive impairment of schizophrenia.

Methods

Subjects

Adult (age range 4–16 months) female Sprague-Dawley rats (Charles River Labs, Raleigh, NC, USA) were used. Rats were housed in groups of two in plastic cages with corn cob in an animal colony room with 12L: 12D light schedule (light on at 7:00 PM). Room temperature was controlled at $21 \pm 2^\circ \text{C}$ and humidity of $50\% \pm 10$. Rats had free access to water in their home cage and were fed daily after testing in order to maintain approximately 85% of their *ad lib* body weights. All training and testing sessions were performed between 8:00 AM and 5:00 PM during the dark phase of the circadian cycle. The treatment and care of the animals were carried out under a protocol approved by the Animal Care and Use Committee of Duke University in an AAALAC-approved facility.

Drug Preparation

Solutions of anabasine, anatabine and dizocilpine (Sigma, St. Louis, MO, USA) were prepared in pyrogen-free glassware in sterilized isotonic saline. All drug doses were given as the salt weight. Acute subcutaneous (SC) injections of anabasine, anatabine, dizocilpine or placebo were given in a volume of 1 ml/kg 20 minutes before the beginning of the test session. Drug treatments were given following a repeated measures counterbalanced design with at least two days between treatments.

Experiments

One group of rats ($N=12$) was trained on the radial-arm maze test of working and reference memory and underwent tests of an acute dose-response of anabasine (0.02, 0.2, 1 and 2 mg/kg) and then anatabine (0.02, 0.2, 1 and 2 mg/kg). Then, two doses of anabasine (0.2 and 2 mg/kg) and anatabine (0.2 and 2 mg/kg) were tested alone or in combination with the glutamate NMDA antagonist dizocilpine (0.05 mg/kg). The saline vehicle was used as vehicle control and dizocilpine alone was used as an impaired control. All conditions were given to each rat in a repeated measures counterbalanced design.

A second set of rats ($N=12$) was trained on the operant visual detection task for assessing attention. After training and establishing a reliable stable baseline, rats were first tested with a dose range of anabasine (0.02, 0.06, 0.2, 1 and 2 mg/kg) with and without dizocilpine (0.0625 mg/kg). Then they were tested with a dose range of anatabine (0.02, 0.06, 0.2, 1 and 2 mg/kg) with and without dizocilpine (0.0625 mg/kg). The saline vehicle was used as vehicle control and dizocilpine alone was used as an impaired control. All conditions were given to each rat in a repeated measures counterbalanced design.

16-Arm Radial Maze Memory Task

Rats were trained in the radial-arm maze. The wood maze was painted black and was at an elevation of 30 cm above the floor, in a room with numerous fixed visual cues. The central platform had a diameter of 50 cm, with 16 arms (10 × 60 cm) projecting radially outward. Each arm contained a food cup 2 cm from the distal end. Rats were given two shaping sessions in which they were placed individually in a large, opaque cylinder on the platform of the maze, given food reinforcement (halves of sugar coated cereal, Froot Loops®, Kellogg's, Battle Creek, MI, USA), and allowed 10 min to eat. The rats were then trained in the radial-arm maze. The same 12 arms were baited for each rat once at the beginning of each session to assess working memory, while the other four arms were always left unbaited to test reference memory in subsequent sessions. The pattern of baited and unbaited arms was consistent throughout testing for each rat but differed among rats. Each trial began by placing the rat in an opaque cylinder on the central platform for 10 s to allow for orientation and thus avoid introducing bias as to which arm would be entered first. The rat was then allowed to enter any arm. The session lasted for up to 10 min, or until all 12 baited arms were entered. Arms were baited only once and a repeated entry into a baited arm was counted as a working memory error, whereas entrance into an unbaited arm was recorded as a reference memory error. Latency (seconds per arm entry) was calculated as the total session time in seconds divided by the total number of arms entered. The animals were trained for 18 sessions in the maze, three times per week per week, and cleaning the maze in between animals with a damp paper towel.

Operant Visual Signal Detection Task

The operant conditioning chambers 29 high × 25 wide × 29 deep cm were equipped with a signal light; a house light; two retractable levers which inserted horizontally 2.5 cm into the chamber; a food cup in the center of the front panel of the chamber (Coulbourn Instruments, Lehigh Valley, PA, USA); and a white noise amplifier (Med Associates Inc, Georgia, VT, USA) mounted above the blank lever generating background white noise of about 65 dB. The signal, or cue light, was located above the food cup. The duration of signal light was set at 500 msec. Signals were generated using Windows based Med Associates Inc. software running on a Pentium computer processor.

Animals were trained to perform visual signal detection task. The task was conducted in 240-trial sessions. Two trial types, "signal" and "blank", were presented in equal number of times per session, in groups of four (2 signal and 2 blank, in random order). Three light intensities (128, 181 and 255 lux) were used. 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 seconds. Immediately following the signal a post-signal interval of 2, 3 or 4 seconds selected randomly occurred. Blank trials were presented identical to the signal trials but without a signal light.

Each trial began with both levers retracted from the chamber first. Then, at the end of the post-signal interval, both levers were inserted into the chamber simultaneously. At this point, the levers were both retracted if the rat pressed one of them or if 5 sec elapsed without a response. If the rat did not press a lever, a response failure was recorded and that particular

trial was not repeated. 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 the 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 sec period of darkness (time out). The left lever was defined as the signal lever for half the rats and the right lever as the blank lever; the opposite assignment was made for the remaining rats.

Statistical Analysis

The following dependent variables were taken in each experiment: for the memory task number of errors and latency to enter and for the attention task percent hit, percent correct rejection, latency and response omissions. The Superanova/Statview computer program (SAS; Cary, NC, USA) was used for the statistical analysis. As directed by the classic statistical text Snedecor and Cochran (Snedecor and Cochran, 1967), interactions with $p < 0.10$ were followed up by tests of the simple main effects. In all cases the final threshold for significance was $p < 0.05$.

Results

16-Arm Radial Maze Memory Task

When given alone to well trained animals neither anabasine nor anatabine over a dose range of 0.02 to 2 mg/kg significantly affected working memory, reference memory or response latency in the radial-arm maze (data not shown). However, as shown in figure 1, when working memory choice accuracy was significantly ($p < 0.025$) impaired with the NMDA glutamate antagonist dizocilpine (0.05 mg/kg), anabasine significantly reversed the impairment at the 0.2 mg/kg ($p < 0.05$) and 2 mg/kg doses ($p < 0.025$). In contrast, anatabine did not significantly attenuate the dizocilpine-induced impairment. At the higher dose of 2 mg/kg anatabine slightly improved working memory, but not significantly (Fig. 1). Reference memory in the radial-arm maze (Fig. 2) was significantly ($p < 0.05$) impaired as a main effect by dizocilpine. None of the dose comparisons were significant. Response latency (Fig. 3) was significantly ($p < 0.01$) quickened as a main effect by dizocilpine. Comparisons of the individual drug doses showed that dizocilpine alone caused a significant ($p < 0.025$) quickening relative to control, but none of the other dose comparisons were significant. Neither anabasine nor anatabine had any significant effects on response latency when administered alone (Table 1).

Operant Visual Signal Detection Task

Dizocilpine also caused significant impairments in attentional accuracy. As shown in figure 4 in the first study with the attention task, dizocilpine (0.0625 mg/kg) significantly ($p < 0.005$) reduced percent correct choice accuracy as a main effect. The individual dose comparisons showed that compared with control dizocilpine when given alone caused a significant ($p < 0.025$) impairment. None of the anabasine doses significantly attenuated this effect. The 0.06 mg/kg anabasine dose, in fact, significantly ($p < 0.05$) exacerbated the dizocilpine-induced impairment. A slight added decrease was also seen with 0.2 mg/kg anabasine but this was not significantly different from dizocilpine alone. None of these

anabasine doses affected choice accuracy on their own. Finer grained analysis of percent hit and percent correct rejection was conducted. The percent hit analysis showed that there was a significant ($p<0.025$) main effect of dizocilpine reducing accuracy. None of the individual dose comparisons were significant with percent hit. There was a significant ($p<0.0005$) main effect of signal light intensity with more accurate performance with brighter signal intensity, but there were no significant interactions with drug treatment. With percent correct rejection there was also a significant ($p<0.05$) dizocilpine main effect of reduction of percent correct rejection. None of the individual dose comparisons was significant.

Response latency was lengthened by dizocilpine as evidenced by a significant ($p<0.001$) main effect. Without dizocilpine the overall average response latency was 73.8 ± 2.1 msec, while with dizocilpine the overall average response latency was 102.0 ± 3.5 msec. There were no other significant drug effects on latency. The number of nonresponse trials was increased by dizocilpine as indicated by a significant ($p<0.025$) main effect with an overall average of 1.2 ± 0.4 non-response trials per session when no dizocilpine was given vs. and overall average of 3.4 ± 0.7 non-response trials per session when dizocilpine was given. There was also a significant dizocilpine $\times$ anabasine interaction ($p<0.05$). Individual dose comparisons showed that the 0.06 mg/kg anabasine dose plus dizocilpine (6.7 ± 2.6) caused a significant ($p<0.05$) increase in non-response trials compared with dizocilpine alone (2.1 ± 0.8). None of the other dose comparisons were significant for the non-response measure.

In the subsequent study testing anatabine (Fig 5), dizocilpine (0.0625 mg/kg) also significantly ($p<0.0005$) reduced overall percent correct choice accuracy as a main effect and with the individual dose comparisons of control vs. dizocilpine alone. Anatabine was effective in significantly attenuating the dizocilpine-induced attentional impairment at the doses of 0.06 mg/kg ($p<0.025$), 1 mg/kg ($p<0.005$) and 2 mg/kg ($p<0.025$). The improved choice accuracy caused by anatabine relative to dizocilpine alone was not complete, but it was significant. None of the anatabine doses improved choice accuracy when given alone. Finer grained analysis of percent hit and percent correct rejection was conducted. The percent hit analysis showed that there was a significant ($p<0.005$) main effect of dizocilpine reducing accuracy. Individual dose comparisons showed that compared with control dizocilpine alone caused a significant ($p<0.005$) impairment (Control= 89.7 ± 1.8 vs. dizocilpine= 80.0 ± 2.5). The only anatabine dose that significantly ($p<0.05$) attenuated this dizocilpine-induced percent hit impairment was 2 mg/kg (86.1 ± 2.7). None of the anatabine doses altered percent hit when given alone.

As with anabasine there was a significant ($p<0.0005$) main effect of signal light intensity with more accurate performance with brighter signal intensity, but there were no significant interactions with drug treatment. The percent correct rejection analysis showed that there was also a significant ($p<0.001$) main effect of dizocilpine reducing accuracy. Individual dose comparisons showed that compared with control, dizocilpine alone caused a significant ($p<0.0005$) percent correct rejection impairment (Control= 95.8 ± 0.8 , Dizocilpine= 84.9 ± 2.7). None of the individual doses of anatabine significantly affected the dizocilpine induced impairment or altered percent correct rejection when given alone.

Latency was increased by dizocilpine as it was in the anabasine study. The main effect of dizocilpine was significant ($p < 0.025$) with latency averaging 70.8 ± 2.0 without dizocilpine and 110.5 ± 5.2 with dizocilpine. The number of nonresponse trials was increased by dizocilpine as indicated by a significant ($p < 0.01$) main effect with an overall average of 0.9 ± 0.3 non-response trials per session when no dizocilpine was given vs. and overall average of 4.2 ± 0.6 non-response trials per session when dizocilpine was given.

Discussion

Nicotine has been found in our studies and others' to significantly improve memory and attentional function (Buccafusco et al., 1999; Elrod et al., 1988; Levin et al., 1992; Rezvani et al., 2002; Rezvani and Levin, 2001). A variety of pharmaceutical companies and academic laboratories are developing nicotinic agonists for treatment of a variety of cognitive impairments such as attentional and memory impairments seen with Alzheimer's disease, schizophrenia and attention deficit hyperactivity disorder (ADHD) (Terry et al., 2011). Indeed, although reports are somewhat mixed, there is evidence that varenicline, the only nicotinic ligand currently approved by FDA for smoking cessation, may improve working memory performance, particularly during periods of abstinence in smokers (Loughead et al., 2010; Patterson et al., 2009). The current studies show that naturally occurring nicotinic agonists such as anabasine and anatabine, which like nicotine are found in tobacco, are effective in improving memory and attentional impairments. Each compound had distinct cognitive effects.

Differential effects were seen with anabasine and anatabine with regard to memory and attentional effects. Anabasine, but not anatabine, significantly reversed dizocilpine-induced memory impairment. These effects on cognitive function were relatively specific inasmuch as neither anabasine nor anatabine affected dizocilpine effects on response latency in the memory or attention tasks. With attentional impairment caused by dizocilpine the reverse was true. Anatabine but not anabasine significantly reversed dizocilpine-induced impairment. In previous studies (Levin et al., 1998; Rezvani et al., 2008; Rezvani and Levin, 2003) we found that nicotine reversed both dizocilpine-induced impairments in memory and attention. While the nAChR binding profile for anabasine has been fairly well investigated, as of this writing there are no published studies regarding the full nAChR binding profile of anatabine. Nonetheless, it is likely that there are differences in the nAChR pharmacology between the two compounds that may explain the differential cognitive effects we observed. Consistent with this hypothesis, in a separate study Clemens et al observed differences in locomotor effects in rats between anabasine and anatabine when combined with nicotine (Clemens et al., 2009). Clemens et al observed that combining anatabine with nicotine significantly increased general locomotor activity compared to nicotine alone, a difference that was not observed when combining anabasine with nicotine. Viewed in light of what is currently known regarding specific nAChR subtypes and behavior, these results would suggest that anatabine may have greater affinity than anabasine for $\alpha 6^*$ and $\beta 2^*$ containing nAChRs (Drenan et al., 2010; Drenan et al., 2008; Quik and McIntosh, 2006). However, a full characterization of anatabine's nAChR profile is needed at this time. Differential effects of anabasine and anatabine on other nicotinic receptor subtypes such as $\alpha 3\beta 4$ and $\alpha 7$ receptors or induced release of transmitters such as catecholamines (dopamine and

norepinephrine), other monoamines (serotonin and histamine) or amino acid transmitters (GABA and glutamate) may also explain their differential effects on memory and attention.

Our data may provide further support for the “self-medication hypothesis” of cigarette smoking that has been posited to explain the very high incidence of smoking among individuals with degraded cognition as people with schizophrenia, ADHD, and even Alzheimer’s disease (Kumari and Postma, 2005; Sacco et al., 2004). It is believed that these individuals smoke largely to alleviate the cognitive deficits that occur as a result of these disorders. Nicotine has always been considered to be the driver of this phenomenon. However, the current evidence suggests that it is more than just the nicotine contained in tobacco that is helping to remediate the cognitive deficits observed in these disorders. Finally, our data provide evidence that the inclusion of anatabine or anabasine in tobacco cessation treatment strategies may be useful in combating the cognitive impairments associated with tobacco withdrawal (Ashare et al., 2014; Hatsukami et al., 1989; Hughes et al., 2007; Teneggi et al., 2005).

Predictive validity of the animal models of memory and attention used in these experiments has been demonstrated. For example, methylphenidate (Ritalin[®]) has been shown in the operant signal detection task to significantly reverse choice accuracy impairments caused by the NMDA glutamate antagonist dizocilpine as well as the muscarinic acetylcholine antagonist scopolamine and the nicotinic antagonist mecamylamine (Rezvani et al., 2009). Nicotine also has been shown to improve accuracy on this task (Rezvani et al., 2002; Rezvani et al., 2006; Rezvani and Levin, 2004; Turchi et al., 1996). Nicotine also improves memory in the radial arm maze task and also attenuates pharmacologically- induced impairment of performance of the task (Levin et al., 1998). Both of these tasks have been shown to heavily rely on $\alpha 4\beta 2$ and $\alpha 7$ nAChR involvement, particularly in the hippocampus (Felix and Levin, 1997; Levin et al., 2002; McGaughy et al., 1999). Blockade of NMDA glutamate receptors with dizocilpine is a reliable model of the cognitive impairment for testing candidate drugs for the improvement of impaired cognition such as memory and attention.

Differential receptor actions of anabasine and anatabine may explain their differential effects on memory and attentional impairments caused by dizocilpine. Anabasine has more pronounced agonist effects at the nicotinic $\alpha 7$ receptor subtype. Anabasine has been found to reverse the dizocilpine induced popping behavior in mice, which is a model of schizophrenia-like behavior (Mastropaolo et al., 2004). Both nicotine and NMDA receptors are ligand gated ion channels with some shared ligand activity. We are not published reports of aware of direct effects of anabasine or anatabine on NMDA glutamate receptors, which are blocked by dizocilpine.

The concentration of anabasine and anatabine in tobacco is quite low compared to nicotine. The higher range of the doses tested in these studies is more than delivered by smoking. The relevance of these studies is not only related to delivery of anabasine and anatabine via tobacco use but also their potential for therapeutic use when given alone. The attenuation of memory and attentional impairments by these compounds in the current studies suggests that

further investigation is in order to determine their therapeutic promise for treating cognitive impairment.

All together, these data show that anabasine and anatabine can improve pharmacologically-induced impaired memory and attention, respectively. Thus here may be an opportunity to use anabasine and anatabine therapeutically especially for people with deficiencies in memory and attention. A convincing argument can be made that so many individuals with schizophrenia smoke because it alleviates their cognitive deficits. Using anabasine and anatabine for memory and attentional enhancement could potentially be an effective avenue for reducing the considerable harm that is caused by tobacco smoking.

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Figure 1.

Anabesine and anatabine interactions with dizocilpine and working memory in the radial-arm maze. In both panels the control and dizocilpine alone data are the same. Data represent mean±sem, N=12. Dizocilpine alone caused a significant ($p<0.025$) increase in working memory errors. This impairment was significantly reversed by 0.2 mg/kg ($p<0.05$) and 2 mg/kg ($p<0.025$) of anabesine, but anatabine at these doses was not observed to produce a significant reduction in errors caused by dizocilpine.

Figure 2.

Anabesine and anatabine interactions with dizocilpine and reference memory in the radial-arm maze. In both panels the control and dizocilpine alone data are the same. Data represent mean $\pm$ sem, N=12. There was a significant main effect of dizocilpine increasing reference memory errors ($p < 0.01$), but there were no significant effects of these doses of anabesine or anatabine on reference errors.

Figure 3.

Anabasine and anatabine interactions with dizocilpine and latency in the radial-arm maze).

In both panels the control and dizocilpine alone data are the same. Data represent seconds per arm entry mean $\pm$ sem, N=12. There was a significant main effect of dizocilpine quickening response ($p < 0.005$), but there were no significant effects of these doses of anabasine or anatabine on response speed.

Figure 4.

Anabasine interactions with dizocilpine and attention in the visual signal detection task Data represent percent correct mean $\pm$ sem, N=12. Anabasine did not attenuate the significant ($p < 0.025$) dizocilpine induced impairment. The 0.06 mg/kg anabasine dose significantly ($p < 0.05$) worsened the dizocilpine induced impairment.

Figure 5.

Anatabine interactions with dizocilpine and attention in the visual signal detection task Data represent percent correct mean $\pm$ sem, N=12. Anatabine significantly attenuated the dizocilpine induced impairment ($p < 0.0005$) at doses of 0.06 mg/kg ($p < 0.025$), 1 mg/kg ($p < 0.005$) and 2 mg/kg ($p < 0.025$).

Table 1
Memory and attentional performance with vehicle and doses of anabasine and anatabine (mean±sem).

Radial-arm Maze	Anabasine			Anatabine		
	0	0.2	2	0	0.2	2
Working memory errors	3.9±0.9	5.1±1.2	2.5±0.8	5.8±1.3	2.9±1.0	
Reference memory errors	3.0±0.7	5.0±0.7	2.6±0.4	5.1±1.1	3.0±0.5	
Response latency	17.2±1.6	14.7±1.2	17.3±2.6	16.0±1.9	14.6±1.6	

Attention Task	Anabasine				Anatabine			
	0	0.02	0.06	0.2	1	2		
Percent correct	89.2±1.6	91.3±1.2	92.7±1.1	92.5±1.1	92.1±1.7	92.2±0.9		
Percent Hit	89.2±1.6	86.0±2.5	89.6±0.6	90.6±1.6	91.9±2.0	90.2±2.6		
Percent Correct Rejection	94.7±0.9	95.5±0.8	94.1±1.2	94.4±1.5	93.2±1.0	93.4±1.4		

	Anabasine				Anatabine			
	0	0.02	0.06	0.2	1	2		
Percent correct	87.6±1.4	87.9±1.4	89.1±1.4	87.9±1.4	89.4±1.3	89.1±1.1		
Percent Hit	89.7±1.8	87.9±2.0	88.9±2.0	88.2±1.6	88.6±2.6	89.9±1.2		
Percent Correct Rejection	95.8±0.8	94.7±1.1	96.4±0.9	95.8±0.9	95.6±1.2	94.6±1.7		