ELSEVIER

Pharmacology, Biochemistry and Behavior 70 (2001) 467–474

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Ventral hippocampal α7 nicotinic receptor blockade and chronic nicotine effects on memory performance in the radial-arm maze

Jane H. Bettany, Edward D. Levin*

Neurobehavioral Research Laboratory, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Bell Building Box 3412, Durham, NC 27710, USA

Received 4 February 2001; received in revised form 14 June 2001; accepted 15 June 2001

Abstract

Chronic nicotine administration has been shown to significantly improve working memory. Nicotinic involvement in memory function critically involves the ventral hippocampus. Local ventral hippocampal infusions of the nicotinic antagonists mecamylamine, dihydro-β-erythroidine (DHβE) and methyllycaconitine (MLA) significantly impair working memory. The impairment caused by hippocampal infusion of the α4β2 antagonist DHβE is reversed by chronic systemic nicotine. This study determined the interaction of chronic systemic nicotine with acute ventral hippocampal infusions of the α7 antagonist MLA. Adult female Sprague–Dawley rats were trained on an 8-arm radial maze working memory task. Then they underwent ventral hippocampal cannulation and received sc implants of minipumps delivering nicotine (0 or 5 mg/kg/day for 28 days). Acute ventral hippocampal infusions of MLA (0, 4.88, 14.64 and 43.92 μg/side) were given during 3–4 weeks of chronic nicotine. MLA caused a significant dose-related memory impairment. In the rats not receiving nicotine, the 14.64 and 43.92 μg/side MLA doses caused significant memory impairment. Chronic systemic nicotine exposure did not block the MLA-induced memory impairment. Comparing the current results with MLA with previous results with DHβE, equimolar ventral hippocampal DHβE more effectively impaired memory than MLA, but the DHβE-induced impairment was more effectively reversed by chronic systemic nicotine administration.

Keywords: Nicotinic; Alpha-7; MLA; Memory; Radial-arm maze; Hippocampus

1. Introduction

Cholinergic systems have long been known to be important for working memory (Bartus et al., 1987). In recent years the important role of nicotinic acetylcholine systems in memory function have been shown in experimental animals and humans (Brioni et al., 1997; Decker et al., 1995; Levin, 1992, 1996). Nicotinic receptors in the hippocampus, a region long known to be important for cognitive function (Jarrard, 1995), have been shown in earlier studies to be important for memory. Local hippocampal infusions of either α7 and α4β2 nicotinic receptor antagonists impair working memory function (Felix and Levin, 1997). Chronic systemic nicotine administration reverses the memory impairment caused by acute ventral hippocampal α4β2 nicotinic blockade (Bancroft and Levin, 2000). The involvement of ventral hippocampal α7 receptors with chronic systemic nicotine effects on memory is the subject of the current study. Differential involvement of α7 and α4β2 nicotinic receptors in memory might help in better basic understanding of the neural substrate of memory function as well as in the development of novel treatments for memory dysfunction such as in Alzheimer's disease.

Experimental studies using a variety of research subjects including rats, monkeys and humans have demonstrated improvement in working memory function with the administration of nicotine (Brioni et al., 1997; Jackson et al., 1989; Levin, 1992). Both acute nicotine injections and chronic nicotine infusions were found to improve working memory performance in the radial-arm maze (Levin, 1996; Levin et al., 1997). Chronic subcutaneous infusions of nicotine at doses of 12 and 5 mg/kg/day for 3 to 4 weeks were both shown to significantly improve working memory

* Corresponding author. Tel.: +1-919-681-6273; fax: +1-919-681-3416.

E-mail address: edlevin@duke.edu (E.D. Levin).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00643-8

performance in rats on the radial-arm maze (Levin and Torry, 1995; Levin et al., 1990, 1993, 1996a). These effects were blocked by co-administration of the noncompetitive nicotinic antagonist mecamylamine (Levin and Rose, 1991; Levin et al., 1993). Nicotinic agonists other than nicotine, such as ABT-418 (Decker et al., 1994), lobeline (Decker et al., 1993), dimethylaminoethyl esters (Levin et al., 1995), epibatidine (Levin et al., 1996b), isonicotine and norisonicotine (Levin et al., 1999c), and GTS-21 (Woodruff-Pak et al., 1994) have also been found to be effective in improving memory performance.

Nicotinic receptors are also important for cognitive function in humans. Nicotine-induced improvements are seen more consistently with attentional function. Nicotine has been shown to improve performance in smokers on attentionally demanding vigilance tasks (Provost and Woodward, 1991; Rusted et al., 1994; Warburton, 1992; Wesnes and Revell, 1984). Importantly, attentional improvements have also been found in nonsmokers given nicotine skin patches (Levin et al., 1998). The cognitive dysfunction of Alzheimer's disease has been shown to be accompanied by a dramatic decrease in nicotinic receptors in the cortex and hippocampus (Court and Clementi, 1995; Nordberg, 1993, 1995; Perry, 1995). Nicotine enhances cognition in normal individuals and in patients with Alzheimer's disease (Jones et al., 1992; Newhouse et al., 1996, 1997; Sahakian et al., 1989; White and Levin, 1999; Wilson et al., 1995). The further definition of both the behavioral and pharmacological nature of nicotinic systems and receptor subtypes in cognitive function is important for a more complete description of the basis of cognitive function and for the possible development of therapeutically useful nicotinic drugs with fewer side effects.

The particular brain areas and nicotinic receptor subtypes responsible for nicotinic involvement in cognitive function are being determined with the techniques of selective lesions and local area drug infusion. These studies have pointed to the hippocampus as a critical site for nicotinic effects on cognitive function. Studies have shown marked increases in levels of hippocampal acetylcholine in rats during learning (Fadda et al., 1996). Hippocampal nicotinic receptors are important in the sensory gating function of the hippocampus (Luntz-Leybman et al., 1992). Local infusions of the general nicotinic antagonist mecamylamine into the hippocampus caused impairments in memory function (Kim and Levin, 1996; Ohno et al., 1993). Local infusions of the $\alpha4\beta2$ nicotinic antagonist dihydro-β-erythroidine (DHβE) or the $\alpha7$ antagonist methyllycaconitine (MLA) into the ventral hippocampus impaired working memory function as measured on the 8-arm radial maze in rats (Felix and Levin, 1997; Levin et al., 2001). Recently, we found that the memory impairment caused by nicotinic $\alpha4\beta2$ blockade in the ventral hippocampus with DHβE is reversed by chronic systemic nicotine infusion (Bancroft and Levin, 2000). The reversibility of the memory impairment caused by $\alpha7$ antagonist hippocampal infusion was the focus of the current study.

$\alpha7$ Nicotinic receptors are found in high concentrations in the rat hippocampus. They are found on hippocampal interneurons with a particularly high density in the CA3 region and dentate granule layer (Court and Clementi, 1995). The functional role of nicotinic $\alpha7$ receptors is still under investigation. Selective stimulation of $\alpha7$ nicotinic acetylcholine receptors has been shown to improve memory in rats (Arendash et al., 1995; Levin et al., 1999a; Meyer et al., 1997). It is thought that the hippocampus is the critical site for this effect. Stimulation of $\alpha7$ nicotinic acetylcholine receptors has implicated them in hippocampal long-term potentiation, a cellular model of memory (Hunter et al., 1994), and sensory gating, a hippocampal-based form of neural habituation (Stevens et al., 1998). Recent studies suggest that the $\alpha7$ nicotinic receptor may play important roles in schizophrenia and neurodegeneration (Alder et al., 1992; Meyer et al., 1994). Significant improvements in working memory in rats were found with administration of the $\alpha7$ specific agonist AR-R 17779. This drug overcame the memory impairments caused by fimbria–fornix knife-cut lesions (Levin et al., 1999a).

MLA is a competitive $\alpha7$ antagonist extracted from the seeds of *Delphinium brownii*. It is a potent competitive inhibitor of nicotinic receptors. Infusions of 2.63–78.7 μg/side of MLA into the ventral hippocampus of rats resulted in dose-related memory impairment on the 8-arm radial maze (Felix and Levin, 1997). The dose of 78.7 μg/side produced a significant deficit in RAM choice accuracy performance, but this very high dose may not have had totally specific effects. Wet dog shakes, a type of preconvulsant activity, were reported at doses as low as 26.3 μg/side. Wet dog shakes are thought to be reliable indicators of limbic seizures or generalized convulsions at higher doses (Rondouin et al., 1997). However, in subsequent studies it has been found that lower doses of ventral hippocampal MLA will also cause significant working memory impairment (Levin et al., 2001).

This study is designed to further the work carried out in a previous study by Bancroft and Levin (2000). The aim of that study was to determine the importance of $\alpha4\beta2$ receptors within the ventral hippocampus for the cognitive effects of chronic nicotine treatment. DHβE significantly decreased the choice accuracy of the control rats whereas no deficit was seen in chronically nicotine-treated rats. The purpose of this study was to determine the involvement of ventral hippocampal $\alpha7$ nicotinic receptors in the nicotine-induced improvement of working memory function in rats. By using the $\alpha7$ specific antagonist MLA at low doses to ensure specificity, the results should give an insight into the mechanism by which nicotine functions and provide further data as to the possible therapeutic value of nicotine to attenuate memory impairment.

2. Methods

2.1. General design

This study was conducted under protocols approved by the Duke University Animal Care and Use Committee. MLA was used to assess the importance of hippocampal $\alpha 7$ receptors in the memory improvement induced by chronic nicotine infusion. The rats were first trained to asymptotic levels of choice accuracy (entries to repeat, ETR) on the 8-arm radial maze (a test of working memory). Then local infusion cannulae were implanted bilaterally into the ventral hippocampus using stereotaxic techniques and 28-day osmotic pumps were implanted subcutaneously to provide the chronic infusions of nicotine. Adverse effects due to surgery were assessed through a short period of postsurgery training on the maze. Vehicle (artificial cerebrospinal fluid, aCSF) and three different concentrations of MLA were acutely infused over the following 2 weeks to each rat and the effects were assessed on the maze. The rats were then sacrificed and cannula placement verified using histological techniques.

2.2. Subjects

Twenty-three adult female Sprague–Dawley strain rats (Taconic Farms, Germantown, NY, USA) weighing between 150–200 g were used. They were housed in a rat colony room with a reverse 12-h light/12-h dark cycle, with lights on at 18:00 h. All behavioral testing was carried out during the dark phase, which is their most active period. The rats were kept in groups of three per cage during the initial RAM training phase, then singly after cannulation. They had ad-libitum access to water with restricted feeding after testing each day to maintain body weight at approximately 85% of free feeding levels.

2.3. Radial-arm maze training

The radial-arm maze can be used to assess working memory. It consists of a 50-cm diameter central platform elevated 30 cm from the floor with eight 10×60 cm arms extending radially, each with a food cup 2 cm from the distal end. The maze is made from black painted wood and housed in a soundproof room with many extra-maze visual cues.

Gentling of the rats consisted of two 5-min periods of handling. The rats were then shaped by placing each in an opaque cylinder in the middle of the maze with eight half pieces of Froot Loops® (a sugar-coated cereal) and giving them up to 5 min to eat all the pieces. Shaping was carried out twice to accustom the rats to the maze.

Radial-arm maze training was then carried out 4 to 5 days a week for at least 18 sessions per rat. Each of the eight arms of the maze was baited with a reinforcer (half a Kellogg's Froot Loop®). The rat was then placed in an opaque cylinder in the middle of the maze for 10 s to allow for orientation and to avoid biased arm entry. Timing began when the cylinder was removed. The rat was allowed to roam freely about the maze for 5 min or until all eight arms had been entered. Arm choice was recorded if all four paws crossed the threshold of the arm. A note was also made if the cereal was eaten. The arms were not rebaited, so repeat entries into an arm were not rewarded and were counted as errors. The choice accuracy, or ETR, the number of arm entries until an error was made, was recorded with a maximum of 8. Response latency (seconds/entry) was calculated by dividing the total time of the session (seconds) by the number of arms entered. The rats were cannulated after 18 training sessions or when they consistently scored high ETRs (6–8). The same protocol was carried out for post-MLA-infusion maze sessions.

2.4. Cannulation

For the acute local drug infusions into the hippocampus, the rats were bilaterally implanted with stainless steel guide cannula (22 gauge, Plastics One, Roanoke, VA, USA) in the ventral hippocampus by stereotaxic surgery. An intraperitoneal injection of 75 mg/kg ketamine mixed with 0.3 mg/kg medetomidine was given to the rats as an anaesthetic prior to surgery. A stereotaxic heating pad was used to maintain the rat's body temperature. The rat's head was then shaved and secured in the stereotaxic apparatus (David Kopf Instruments, Tajunga, CA, USA) with ear bars and bite bar elevating the head to +5 mm above the intra-aural line. A small incision was made from between the eyes to between the ears and bregma was located. The coordinates for the ventral hippocampus as described in the rat brain atlas by Pellegrino et al. (1979) were used for the internal cannula tips. They are AP −3.2, ML ±5.5, DV −7.0 mm calculated from bregma. The guide cannulae were lowered through holes drilled through the skull and fixed in place using cranioplastic cement anchored to four skull screws with stainless steel wire wrapped around them.

2.5. Chronic nicotine treatment

Chronic nicotine was delivered to the rats via subcutaneously implanted osmotic pumps (Alzet Model 2ML4, Alza, Palo Alto, CA). These were filled with 2 ml of nicotine solution calculated to deliver nicotine at a rate of 5 mg/kg/day over a 28-day period. The pumps were implanted immediately after surgery, while the rat was still under anaesthetic and sealed in using staples at the top of its back. Chronic nicotine infusions were used because these provide continual zero order kinetic delivery of nicotine. This route and delivery regimen has been found in our previous studies to cause significant memory improvement (Levin and Torry, 1995; Levin et al., 1990, 1993, 1996a,b) and reversal of memory impairment due to ventral hippocampal infusion of DHβE (Bancroft and Levin, 2000). The rats were continually infused with the

implanted minipump and thus did not need to be handled during chronic nicotine infusion.

Antisedan was administered to the rats after the surgical procedures to counteract the effects of the medetomidine. The rats were given a week to recover after the surgery. During this period the weight and diet of each rat was carefully monitored for adverse effects due to surgery. After 1 week the rats were given a test run on the maze to check for decreases in performance.

2.6. Acute MLA administration

Two test doses of aCSF were given to each rat in the second week after surgery to accustom the rats to the

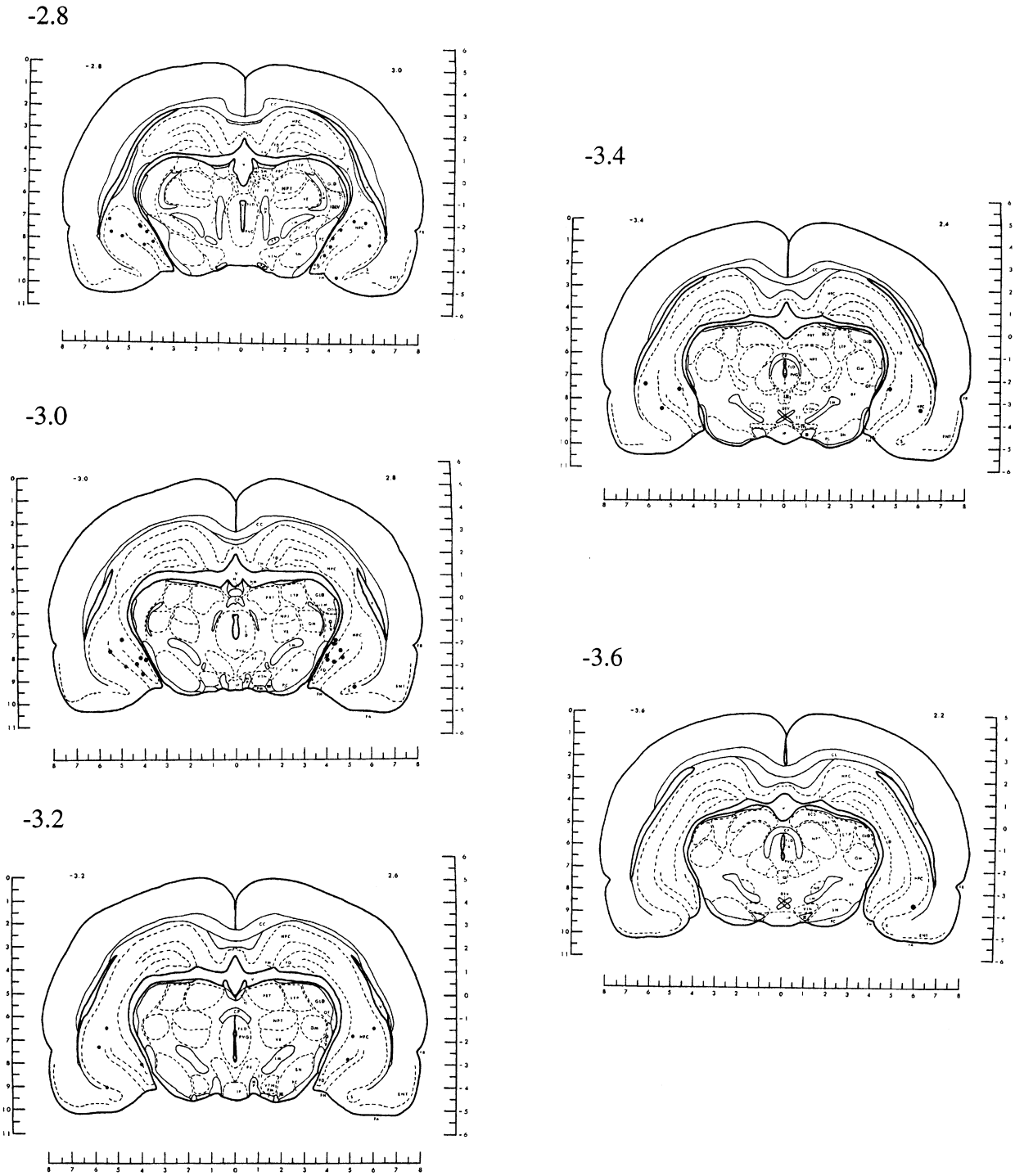

Fig. 1. Cannula placements within the ventral hippocampus at an AP coordinate of −2.8, −3.0, −3.2, −3.4 and −3.6 mm according to the atlas of Pellegrino et al. (1979).

procedure. Over the ensuing 2 weeks, four doses of MLA were administered in a counterbalanced design, two in the third week and two in the fourth week to establish a dose–response curve. The doses used were 0, 4.88, 14.64 and 43.92 μg/side (where aCSF was used). These were equimolar to doses of DHβE (0, 2, 6 and 18 μg/side) used previously. These doses were made by taking samples from a stock solution of MLA dissolved in aCSF and diluting them to the required concentration with aCSF. 0.2 μl of drug/vehicle was infused per side of the brain at a rate of 0.126 μl/min using a Harvard Instruments infusion pump. The rats were run on the maze 10 min after infusion.

2.7. Histology

Following completion of the drug-dosing phase, each rat was anaesthetized with sodium pentobarbital (50 mg/kg). Chicago sky blue dye (0.5 μl) was infused to mark cannula placement. Perfusion was carried out with saline followed by 0.1 M (4%) formaldehyde. The brains were stored in 4% formaldehyde until slicing. Before slicing the brains were washed in dH_20, the cerebellum sliced off ready for mounting and frozen on dry ice. A Jung 2000 cryostat was used to prepare histological slides, which were used to verify and record cannula placement.

2.8. Data analysis

The choice accuracy and response latency measures were assessed by a within subjects design analysis of variance (ANOVA). Planned comparisons were made between the saline only and nicotine treatment groups at each dose of MLA. A P value of $<.05$ (two-tailed) was considered significant.

3. Results

3.1. Histology

Cannula placements were verified histologically. Only those rats with accurate bilateral placements in the ventral hippocampus were used for statistical analysis of the behavioral data. Placements used were between coordinates A/P −2.8 to −3.6 mm, M/L 3.8 to 6.1 mm and D/V −6.5 to −9.4 mm. The cannula placements are shown in Fig. 1A–E. Each figure shows a coronal section of the brain at a different anterior–posterior coordinate (from −2.8 to −3.6). Some rats had different AP placements for the left and right side so each plane of section has an unequal number of placements on the left and right sides.

3.2. Radial-arm maze choice accuracy

There was a significant main effect of MLA dose on memory performance [$F(3,57)=6.57$, $P<.001$]. Averaged across nicotine treatment groups, compared to performance with control infusions (6.78±0.30 ETR±S.E.M.), there was no significant impairment caused by the lowest dose of 4.9 μg/side (6.46±0.33); however, there were significant ($P<.005$) memory deficits induced by the 14.6 μg/side (5.61±0.42) and the 43.92 μg/side (5.52±0.42) MLA doses. As shown in Fig. 2, significant linear MLA dose-related impairments were seen in rats administered nicotine ($P<.05$) as well as controls ($P<.005$). Pair-wise comparisons of performance after the aCSF hippocampal infusion vs. each of the MLA doses for nicotine-treated rats and controls showed that with concurrent systemic nicotine administration only the highest 43.92 μg/side MLA dose caused a significant ($P<.05$) memory impairment. The controls showed significant impairments with both the medium 14.6 μg/side dose ($P<.025$) and the highest 43.92 μg/side dose ($P<.025$). However, at no dose of MLA was there a significant difference between performance of the rats given nicotine and those not given nicotine. Analysis of the linear and quadratic trends showed a very significant linear trend of worse choice accuracy with higher doses of MLA ($P<.0005$). However, the quadratic trend over MLA dose was not significant ($P=.79$). Comparison of chronic nicotine and no nicotine treatment groups with regard to trends over acute hippocampal MLA dose did not show any hint of significant differences in the linear ($P=.66$) or quadratic ($P=.87$) trends.

3.3. Radial-arm maze response latency

Neither chronic nicotine treatment nor acute MLA treatment significantly affected response latency in the radial-arm maze. One outlier in the no nicotine group with a latency of 300 after 14.6 μg/side MLA was removed from the analysis. The 43.9 μg/side dose of MLA nicotine-treated rats averaged 29.9±3.4 s/entry,

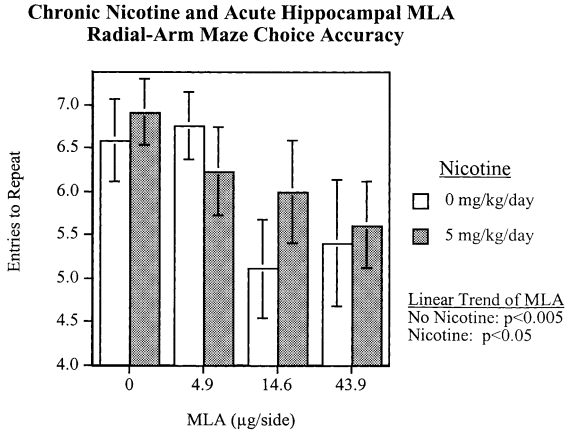

Fig. 2. The radial arm maze choice accuracy (mean±S.E.M.) for the nicotine (5 mg/kg/day) and control (saline) rats at vehicle (aCSF) and three doses of MLA (4.9, 14.6 and 43.9 μg/side).

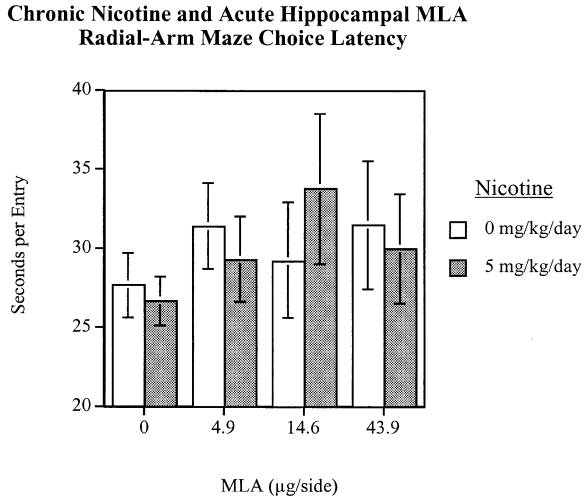

Fig. 3. A graph showing the radial-arm maze choice latency (mean ± S.E.M.) for the nicotine (5 mg/kg/day) and control rats (saline) at vehicle (aCSF) and three doses of MLA (4.9, 14.6 and 43.9 μg/side).

whereas the 0 μl/side of MLA (aCSF) nicotine-treated rats averaged 26.6 ± 1.6 s/entry. Without nicotine, these figures were 31.4 ± 4.1 s for the 43.9 μg/side dose of MLA and 27.6 ± 2.0 for aCSF (Fig. 3).

3.4. Wet dog shakes

No wet dog shakes were seen at any of the doses of MLA used.

4. Discussion

Replicating our previous work (Felix and Levin, 1997; Levin et al., 2001), MLA caused a significant dose-related radial-arm maze choice accuracy impairment. The MLA-induced memory impairment was still seen with concurrent chronic systemic nicotine infusion. These results support the hypothesis that ventral hippocampal α7 receptors are critical for memory function and that disruption of these receptors may impair the effectiveness of systemic nicotine treatment. In clinical conditions decreased functioning of hippocampal α7 receptors may contribute to cognitive impairment, and it may also limit the therapeutic efficacy of chronic nicotine treatment.

Chronic nicotine has been demonstrated in a variety of previous studies to improve memory performance of rats in the radial-arm maze (Levin and Rose, 1990; Levin and Torry, 1996; Levin et al., 1993, 1996a). The improvement in choice accuracy was found to persist over 4 weeks of nicotine administration. This persistence of effect is important for its possible use therapeutically. Treatments must maintain their efficacy with chronic administration for the beneficial treatment of chronic conditions. The nicotine-induced memory improvement can be blocked by chronic systemic co-infusion of the nicotinic antagonist mecamylamine (Levin et al., 1993) and by small ibotenic acid lesions in the ventral hippocampus (Levin et al., 1999b).

In the current study, as in our pervious one (Bancroft and Levin, 2000), chronic systemic nicotine treatment was not found to significantly improve memory performance when aCSF was infused. It is possible that the chronic placement of infusion cannulae in the ventral hippocampus caused sufficient neural damage in this area to prevent the chronic nicotine-induced memory improvement. However, this is most likely not the case. The damage caused by cannula placement was minimal. But more convincingly, recently we have found that chronic indwelling cannulae delivering aCSF over a 4-week period did not block a significant ($P < .05$) chronic systemic nicotine- (5 mg/kg/day for 4 weeks) induced memory improvement. Alternatively, the intermittent infusion of nicotinic antagonists in the ventral hippocampus may have prevented the development of the chronic nicotine-induced memory improvement.

Neither response latency nor wet dog shakes were found to be significantly affected by either chronic systemic nicotine or acute ventral hippocampal MLA in the current study. This supports the specificity of the effects seen with these drug treatments on choice accuracy in the radial-arm maze. Higher doses of MLA can cause increases in wet dog shakes and decreases in response latency (Felix and Levin, 1997; Levin et al., 2001).

In our previous study, chronic nicotine reversed the deficits in memory impairment caused by acute hippocampal DHβE (Bancroft and Levin, 2000). When the effectiveness of equimolar doses of DHβE vs. MLA were compared, lower doses of DHβE were found to be more effective. A significant difference was found between the lowest equimolar dose of MLA (4.9 μg/side, 6.76 ± 0.39 ETR) and DHβE (2 μg/side, 4.88 ± 0.52 ETR) [$F(1,17) = 9.93$, $P < .01$]. This suggests that either DHβE is a more potent antagonist than MLA or that the α4β2 receptor is more prominent than the α7 receptor in memory function.

Interestingly, the same systemic chronic dose of nicotine that effectively reversed DHβE-induced memory impairment was not effective in reversing MLA-induced memory impairment. This provides evidence that ventral hippocampal α7 nicotinic receptors seem to be more critical for systemic nicotine effects on memory function than ventral hippocampal α4β2 receptors. The inability of nicotine to reverse the response to MLA may be related to α7 receptor desensitization which is quite rapid. Also, systemically administered nicotine may be acting at other areas besides the ventral hippocampus to overcome the DHβE effects in the hippocampus while this may not be possible with regard to α7 actions. No matter what the mechanism for the effect, nicotine-based therapy may be less effective against memory dysfunction involving hippocampal α7 receptors.

Acknowledgments

This research was supported by The National Institute on Drug Abuse grant no. DA 11943.

References

Alder LE, Hoffer LJ, Griffith J, Waldo MC, Freedman R. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. Biol Psychiatry 1992;32:607–16.

Arendash GW, Sengstock GJ, Sanberg PR, Kem WR. Improved learning and memory in aged rats with chronic administration of the nicotinic receptor agonist GTS-21. Brain Res 1995;674:252–9.

Bancroft A, Levin ED. Ventral hippocampal a4B2 nicotinic receptors and chronic nicotine effects on memory. Neuropharmacology 2000;39: 2770–8.

Bartus RT, Dean RL, Flicker C. Cholinergic psychopharmacology: an integration of human and animal research on memory. In: Meltzer HY, editor. Psychopharmacology: the third generation of progress. New York: Raven Press, 1987. pp. 219–32.

Brioni JD, Decker MW, Sullivan JP, Arneric SP. The pharmacology of (−)-nicotine and novel cholinergic channel modulators. Adv Pharmacol 1997;37:153–214.

Court J, Clementi F. Distribution of nicotinic subtypes in human brain. Alzheimer Dis Assoc Disord 1995;9:6–14.

Decker MW, Majchrzak MJ, Arneric SP. Effects of lobeline, a nicotinic receptor agonist, on learning and memory. Pharmacol Biochem Behav 1993;45:571–6.

Decker MW, Curzon P, Brioni JD, Arneric SP. Effects of ABT-418, a novel cholinergic channel ligand, on place learning in septal-lesioned rats. Eur J Pharmacol 1994;261:217–22.

Decker MW, Brioni JD, Bannon AW, Arneric SP. Diversity of neuronal nicotinic acetylcholine receptors: lessons from behavior and implications for CNS therapeutics—minireview. Life Sci 1995;56:545–70.

Fadda F, Melis F, Stancampiano R. Increased hippocampal acetylcholine release during working memory task. Eur J Pharmacol 1996;307: R1–2.

Felix R, Levin ED. Nicotinic antagonist administration into the ventral hippocampus and spatial working memory in rats. Neuroscience 1997; 81:1009–17.

Hunter BE, de Fiebre CM, Papke RL, Kem WR, Meyer EM. A novel nicotinic agonist facilitates induction of long-term potentiation in the rat hippocampus. Neurosci Lett 1994;168:130–4.

Jackson WJ, Elrod K, Buccafusco JJ. Delayed matching-to-sample in monkeys as a model for learning and memory deficits: role of brain nicotinic receptors. In: Meyer EM, Simpkins JW, Yamamoto J, editors. Novel approaches to the treatment of Alzheimer's disease. New York: Plenum Publishing, 1989. pp. 39–52.

Jarrard LE. What does the hippocampus really do? Behav Brain Res 1995; 71:1–10.

Jones GMM, Sahakian BJ, Levy R, Warburton DM, Gray JA. Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. Psychopharmacology 1992;108:485–94.

Kim J, Levin E. Nicotinic, muscarinic and dopaminergic actions in the ventral hippocampus and the nucleus accumbens: effects on spatial working memory in rats. Brain Res 1996;725:231–40.

Levin ED. Nicotinic systems and cognitive function. Psychopharmacology 1992;108:417–31.

Levin ED. Nicotinic agonist and antagonist effects on memory. Drug Dev Res 1996;38:188–95.

Levin ED, Rose JE. Anticholinergic sensitivity following chronic nicotine administration as measured by radial-arm maze performance in rats. Behav Pharmacol 1990;1:511–20.

Levin ED, Rose JE. Nicotinic and muscarinic interactions and choice accuracy in the radial-arm maze. Brain Res Bull 1991;27:125–8.

Levin ED, Torry D. Nicotine effects on memory performance. In: Clarke PBS, Quik M, Thurau K, Adlkofer F, editors. International symposium on nicotine: the effects of nicotine on biological systems II. Boston: Birkhäuser, 1995. pp. 329–36.

Levin ED, Torry D. Acute and chronic nicotine effects on working memory in aged rats. Psychopharmacology 1996;123:88–97.

Levin ED, Lee C, Rose JE, Reyes A, Ellison G, Jaravik M, Gritz E. Chronic nicotine and withdrawal effects on radial-arm maze performance in rats. Behav Neural Biol 1990;53:269–76.

Levin ED, Briggs SJ, Christopher NC, Rose JE. Chronic nicotinic stimulation and blockade effects on working memory. Behav Pharmacol 1993; 4:179–82.

Levin ED, Rose JE, Abood L. Effects of nicotinic dimethylaminoethyl esters on working memory performance of rats in the radial-arm maze. Pharmacol Biochem Behav 1995;51:369–73.

Levin E, Kim P, Meray R. Chronic nicotine effects on working and reference memory in the 16-arm radial maze: interactions with D1 agonist and antagonist drugs. Psychopharmacology 1996a;127:25–30.

Levin ED, Toll K, Chang G, Christopher NC, Briggs SJ. Epibatidine, a potent nicotinic agonist: effects on learning and memory in the radial-arm maze. Med Chem Res 1996b;6:543–54.

Levin E, Kaplan S, Boardman A. Acute nicotine interactions with nicotinic and muscarinic antagonists: working and reference memory effects in the 16-arm radial maze. Behav Pharmacol 1997;8:236–42.

Levin ED, Conners CK, Silva D, Hinton SC, Meck WH, March J, Rose JE. Transdermal nicotine effects on attention. Psychopharmacology 1998; 140:135–41.

Levin ED, Bettegowda C, Blosser J, Gordon J. AR-R17779, an alpha 7 nicotinic agonist, improves learning and memory in rats. Behav Pharmacol 1999a;10:675–80.

Levin ED, Christopher NC, Weaver T, Moore J, Brucato F. Ventral hippocampal ibotenic acid lesions block chronic nicotine-induced spatial working memory improvement in rats. Cognit Brain Res 1999b;7: 405–10.

Levin ED, Damaj MI, Glassco W, May EL, Martin BR. Bridged nicotine, isonicotine and norisonicotine effects on working memory performance of rats in the radial-arm maze. Drug Dev Res 1999c;46:107–11.

Levin ED, Bradley A, Addy N, Sigurani N. Hippocampal a7 and a4b2 nicotinic receptors and working memory. Neuroscience 2001 (in press).

Luntz-Leybman V, Bickford PC, Freedman R. Cholinergic gating of response to auditory stimuli in rat hippocampus. Brain Res 1992;587: 130–6.

Meyer EM, de Fiebre CM, Hunter BE, Simpkins CE, Frauworth N, de Fiebre NE. Effects of anabaseine-related analogs on rat brain nicotinic receptor binding and on avoidance behaviors. Drug Dev Res 1994;31: 127–34.

Meyer EM, Tay ET, Papke RL, Meyers C, Huang GL, deFiebre CM. 3-[2,4-Dimethoxybenzylidene]anabaseine (DMXB) selectively activates rat alpha 7 receptors and improves memory-related behaviors in a mecamylamine-sensitive manner. Brain Res 1997; 768:49–56.

Newhouse P, Potter A, Corwin J. Effects of nicotinic cholinergic agents on cognitive functioning in Alzheimer's and Parkinson's disease. Drug Dev Res 1996;38:278–89.

Newhouse PA, Potter A, Levin ED. Nicotinic system involvement in Alzheimer's and Parkinson's diseases: implications for therapeutics. Drugs Aging 1997;11:206–28.

Nordberg A. Clinical studies in Alzheimer patients with positron emission tomography. Behav Brain Res 1993;57:215–24.

Nordberg A. Imaging of nicotinic receptors in human brain. In: Domino EF, editor. Brain imaging of nicotine and tobacco smoking. Ann Arbor (MI): Npp Books, 1995. pp. 45–57.

Ohno M, Yamamoto T, Watanabe S. Blockade of hippocampal nicotinic receptors impairs working memory but not reference memory in rats. Pharmacol Biochem Behav 1993;45:89–93.

Pellegrino LJ, Pellegrino AS, Cushman AJ. A stereotaxic atlas of the rat brain. 2nd ed. New York: Plenum, 1979.

Perry E. Cholinergic signaling in Alzheimer disease: therapeutic strategies. Alzheimer Dis Assoc Disord 1995;9:1–2.

Provost SC, Woodward R. Effects of nicotine gum on repeated administration of the Stroop test. Psychopharmacology 1991;104:536–40.

Rondouin G, Lerner-Natoli M, Hashizume A. Wet dog shakes in limbic versus generalized seizures. Exp Neurol 1997;95:500–5.

Rusted J, Graupner L, Oconnell N, Nicholls C. Does nicotine improve cognitive function? Psychopharmacology 1994;115:547–9.

Sahakian B, Jones G, Levy R, Gray J, Warburton D. The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of Alzheimer type. Br J Psychiatry 1989;154: 797–800.

Stevens KE, Kem WR, Mahnir VM, Freedman R. Selective alpha(7)-nicotinic agonists normalize inhibition of auditory response in DBA mice. Psychopharmacology 1998;136:320–7.

Warburton DM. Nicotine as a cognitive enhancer. Prog Neuro-Psychopharmacol Biol Psychiatry 1992;16:181–919.

Wesnes K, Revell A. The separate and combined effects of scopolamine and nicotine on human information processing. Psychopharmacology 1984; 84:5–11.

White HK, Levin ED. Chronic four week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology 1999;143:158–65.

Wilson AL, Langley LK, Monley J, Bauer T, Rottunda S, McFalls E, Kovera C, McCarten JR. Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. Pharmacol Biochem Behav 1995;51:509–14.

Woodruff-Pak DS, Li YT, Kem WR. A nicotinic agonist (GTS-21), eyeblink classical conditioning, and nicotinic receptor binding in rabbit brain. Brain Res 1994;645:309–17.