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Nicotinic antagonist effects in the mediodorsal thalamic nucleus: Regional heterogeneity of nicotinic receptor involvement in cognitive function

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ABSTRACT

Nicotine has been found in many studies to improve cognitive function. However, some studies have not found this effect and others have seen nicotine-induced impairments. Systemic administration bathes the brain with drugs. However, the brain is quite intricately organized with various regions playing very different roles in the bases of cognitive function. We have examined the role of nicotinic receptors in a variety of brain areas for memory. In the hippocampus and amygdala, local infusions of both α7 and α4β2 antagonists methyllyaconitine (MLA) and dihydro-β-erythroidine (DHβE) significantly impair memory. In the current studies we locally infused acute and chronic doses of MLA and DHβE into the mediodorsal thalamic nucleus and tested memory function on a 16-arm radial maze. The rats also received systemic nicotine to determine the impact of more generalized nicotine effects. Since nicotinic treatments are being developed for cognitive impairment of schizophrenia, interactions were studied with the antipsychotic drug clozapine. In the acute study, the 6.75 μg/side of DHβE improved working memory. Co-administration of MLA reversed the DHβE-induced improvement. Chronic DHβE infusions into the mediodorsal thalamic nucleus also improved working memory. Systemic nicotine reversed this effect. Clozapine had no significant interaction. Nicotinic α4β2 receptors in the mediodorsal thalamic nucleus appear to play an opposite role with regard to working memory than those in the hippocampus and amygdala. Heterogeneity in response to nicotinic drugs given systemically may be due to anatomically distinct nicotinic systems in the brain and their unique roles in the neural bases of cognitive function.

1. Introduction

Nicotinic receptor systems have been shown to be important in the neural bases for memory function, however, there is heterogeneity of response to nicotinic treatments for memory improvement [1–7]. The principal findings in the literature are that nicotinic agonists improve memory function, while nicotinic antagonists impair it. However, in some cases the opposite effects have been found, with nicotine causing memory impairment [8–10] and nicotinic antagonists causing improvement [11–13]. The varying systemic nicotinic drug effects on memory function may be due to the diverse brain regions in which nicotinic receptors are located. Nicotinic receptor systems are found in a many different brain regions with distinct functions with regard to memory. It is likely that nicotinic receptors in different regions would have different effects on memory function.

Local infusions have proven to be an effective method for determining the anatomic localization of specific receptor subtypes in cognitive function. In a series of studies, we have used the local infusion technique to determine the involvement of nicotinic receptors in particular brain areas for memory function. The nonspecific nicotinic antagonist mecamylamine infused acutely into the ventral hippocampus [14], substantia nigra and ventral tegmental area [15] produced significant working memory deficits on the radial-arm maze, whereas infusions of the same doses into the nucleus accumbens did not produce an effect on memory [14]. Acute local infusions of either the α7 antagonist MLA or α4β2 antagonist DHβE in the hippocampus significantly impair working memory function [16–20]. Interestingly, when DHβE and MLA were given together they did not produce an additive impairment [19]. Chronic systemic nicotine infusion (5 mg/kg/day) effectively reversed the DHβE, but not the MLA induced memory impairment after ventral hippocampal infusion of these antagonists [17,18]. A higher dose of nicotine or an α7 agonist may be required for

Abbreviations: MLA, methyllyaconitine; DHβE, dihydro-β-erythroidine.

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reversal of α7 blockade-induced impairment because of the low affinity of this nicotinic receptor subtype.

The effect of longer-term reduction of nicotinic receptor action can be determined by attaching slow delivery osmotic minipumps to the local infusion cannulae. Chronic infusion of DHβE in the ventral hippocampus (100 μg/side/day) impaired working memory function in the radial-arm maze, an effect that was decreased by systemic nicotine [21]. Chronic nicotinic antagonist infusion in the hippocampus significantly altered the effects of the antipsychotic drug clozapine on memory function [22]. In the control rats, clozapine caused a significant memory impairment. This effect was exacerbated by chronic hippocampal infusions of MLA. In that study, we replicated the previous finding that chronic hippocampal DHβE infusion (100 μg/side/day) caused memory impairment. This effect was significantly attenuated by clozapine even though clozapine in controls caused a significant memory impairment. In contrast, chronic MLA infusion (83 μg/side/day) did not cause a memory impairment, but it did significantly potentiate the potency of clozapine, with the low clozapine dose causing a significantly greater impairment when given together with hippocampal MLA compared with aCSF infusions.

The medial frontal cortex, in contrast to the hippocampus, plays quite a different role; chronic nicotinic α4β2 blockade in the medial frontal cortex with DHβE infusion at the same dose that impairs memory after hippocampal infusion did not produce a memory impairment but it did potentiate the memory impairment caused by clozapine, opposite the effect seen with hippocampal infusion [23].

In the basolateral amygdala, acute local infusion of DHβE and MLA caused significant working memory impairments on the radial-arm maze [24], although these effects were more modest than those seen with the same doses in the hippocampus. As in the hippocampus these impairments were not additive. In fact MLA was found to significantly attenuate the amnestic effects of DHβE.

The current studies examined the role of α7 and α4β2 nicotinic receptors in the mediodorsal thalamic nucleus with regard to memory function. The thalamus is the site of substantial nicotinic receptor concentration [25]. Several areas of the thalamus have been shown to be important for cognitive function. The mediodorsal thalamic nucleus is in particularly important position having reciprocal direct connections with the frontal cortex [26]. Electrolytic lesions of the mediodorsal thalamic nucleus have been shown to impair memory performance of rats in the radial-arm maze [27].

Nicotinic treatments hold promise for syndromes of cognitive dysfunction such as Alzheimer's disease, attention deficit hyperactivity disorder as well as the cognitive deficits in schizophrenia [28–30]. To facilitate development of nicotinic drugs for cognitive therapy, the field must develop a better understanding how nicotinic receptors in different areas of the brain play diverse roles in cognitive function.

2. Methods

2.1. Design

Two studies were conducted to determine the role of α4β2 and α7 nicotinic receptors in the mediodorsal (MD) thalamic nucleus in memory function. The first study examined the effects of acute administration of an α4β2 antagonist DHβE (0,1.18, 3.38 and 6.75 μg/side) and an α7 antagonist MLA (0 and 6.75 μg/side) on working and reference memory in a 16-arm radial maze. The second study examined the effects of chronic four-week infusions of these antagonists into the MD thalamic nucleus. In the second study interactions of the nicotinic antagonists with systemic administration of nicotine and the antipsychotic drug clozapine were also studied.

2.2. Subjects

Young adult female Sprague-Dawley rats (N = 18 in Study 1 and N = 89 in Study 2) were used. Female rats were used because of the history of using females in the series of studies [22,23] so that the results could be directly compared. Females have been used in this series of studies because with chronic studies they keep a relatively constant weight better than males, with the use of potentially sedative drugs they are more likely to continue to perform on the radial-arm maze and the fact that the majority of people with Alzheimer's disease are female [31]. We did not artificially disrupt the estrus cycle of the rats by removing the ovaries or administering hormones. Rather the chronic study involved repeated testing spanning many estrus cycles with average data analyzed. The rats were maintained on a reverse 12-h on:12-h off light cycle, with all testing conducted during the dark phase. This was done because rats sleep more during the light phase and testing then would introduce greater disruption of their normal sleep cycle. They were housed in metal cages with wood shavings, three rats per cage pre-cannulation and one rat per cage post-cannulation. They had ad lib access to water and were fed approximately 15–20 g/day of Purina rat chow daily following testing. This feeding schedule was kept throughout the shaping, training and experimental periods. Prior to testing, each rat was handled for two sessions of 5–10 min to provide habituation to handling by the experimenter. During this handling period, twelve pieces of bait, half-pieces of the sweetened cereal Kellogg's Froot Loops® (Kellogg, Battle Creek, MI, USA), were provided per animal per day in the housing cages.

2.3. Radial-arm maze testing

Rats were shaped to the maze and food reinforcements by placing them in an opaque ring on the 16-arm radial maze and placing 12 halve pieces of Kellogg's Froot Loops® (Kellogg, Battle Creek, MI, USA) inside the ring. The total number of pieces of Fruit Loops eaten in a 10-min time period was recorded for each subject. After three consecutive shaping sessions rats begin acquisition testing. The 16-arm radial maze was used to assess spatial working memory. The maze consisted of a round circular platform 50 cm in diameter, elevated 30 cm high with 16 arms equidistant in length and width (10 cm × 60 cm) radiating from the center. Each arm was separated by clear Plexiglas barriers. Arms also contained cups (2 cm form the end of the arm) for placement of reinforcing rewards. The maze was located in a room with ample stable extramaze visual cues. Prior to each session, 12 of the 16 cups on the maze were baited with halve pieces of Kellogg's Froot Loops®. Each subject had a different set of baited arms, which remained the same throughout the course of the study. During acquisition training, rats were placed in an opaque ring in the center of the maze for 10 s after which the opaque ring was removed and rats were allowed to roam the maze freely. The total number of entries into an arm was recorded. Choice accuracy was measured by counting the number of working memory errors and reference memory errors. Working memory errors were defined as repeated entries into an initially baited arm. Reference memory errors were defined as repeated entries into an initially unbaited arm. The trial ended when a subject entered into all of the baited arms or a total of 600 s had elapsed.

2.4. Cannulation

Following at least 18 radial-arm maze training sessions during which no drugs were administered, the rats were cannulated in the

mediodorsal thalamic nucleus. The target coordinates from bregma used for the mediodorsal thalamic nucleus were: A/P −1.2, M/L ±1.0, and D/V −5.5 based on the rat brain atlas of Pellegrino [32]. Rats were anaesthetized with an IP injection of 65 mg/kg of ketamine combined with 15 mg/kg of Domitor (medetomidine HCl). The rat was placed on an electric heating pad to maintain body temperature and secured in a stereotaxic instrument (David Kopf instruments, Tujunga, CA, USA) with ear and bite bars that held the head elevated 5 mm above the intra-aural line. Fur was shaved from the rat's head and the skull was exposed with a lengthwise incision. Coordinates were measured from bregma, and appropriate cannulae holes were drilled into the skull. Posterior to these holes, four screws were fixed and tied together with wire to anchor the protective cranioplastic cap that would be built. For Study 1, steel 22-gauge guide cannulae were lowered to the coordinates and cranioplastic cement was applied to secure them and cover the opened area, forming a protective cap. Dummy cannulae were placed in the guide cannulae to prevent infection and blockage. After completion of the surgery, 15 mg/kg of Antisedan (atipamezole HCl) was administered intraperitoneal (IP) to revive the animal. The rats were allowed to rest for a full week after surgery. During the post-surgery period two trials with infusions of artificial cerebrospinal fluid (aCSF) were conducted to adjust them to the infusion procedure. For Study 2 surgical procedures were the same except that infusion cannulae were attached to osmotic minipumps (Alzet Model 2004) via polyethylene tubing. Dental cement was used to anchor cannulae. A pocket was made beneath the skin on the neck to hold the osmotic minipumps into place. Polypro suturing was used in order to secure the minipumps and tubing. Dental cement was used to create a cement cap to protect the cannulae. A pocket was also created beneath the rat's skin on its side in order to hold a larger osmotic pump (Alzet Model 2ML4) to deliver chronic systemic nicotine or saline vehicle. Surgical clips were used to close the pocket and secure the larger osmotic minipump. After surgery rats were allowed one week for recovery before testing sessions resumed on the 16-arm radial maze.

2.5. Drug administration

In Study 1 acute doses of the nicotinic antagonists were administered bilaterally in a repeated measures counterbalanced design. The rats ($N = 18$) were infused with DHβE in doses of 0, 1.18, 3.38, or 6.75 μg/side. Each of these doses of DHβE was administered alone and with 6.75 μg/side of MLA. Drug sessions were conducted with at least two days between tests. The infusions were given at a rate of 0.126 μl/min for a total of 3 min and 10 s. The drugs were pumped through 28-gauge infusion cannulae attached to 10 μl Hamilton syringes by polyethylene tubing. Twenty minutes after the infusion ceased, the rats were tested on the maze.

In Study 2 with chronic infusions there were six total nicotinic drug conditions with three chronic local mediodorsal thalamic nucleus infusions: aCSF (vehicle control), 83 μg/side/day of MLA or 100 μg/side/day of DHβE crossed with two chronic systemic (s.c.) nicotine ditartrate infusions levels (0 or 5 mg/kg/day calculated as of the base weight). Group sizes are listed below.

Group sizes for nicotinic antagonist treatment conditions in the mediodorsal thalamic nucleus.

	Chronic systemic nicotine (mg/kg, s.c.)	
MD Thalamic Infusions	0	5
aCSF	24	19
MLA	12	11
DHβE	11	12

These drugs were infused with osmotic minipumps (Alzet Model 2ML4, infusion rate 2.5 μl/h) for the subcutaneous (s.c.) nicotine infusion and two Alzet Model 2004 pumps for the bilateral local infusions, infusion rate 0.25 μl/h for each pump). The pumps delivering systemic nicotine administration were implanted in a subcutaneous pocket made under the skin between the scapulae. The pumps delivering local infusions of nicotinic antagonists were connected to the infusion cannulae via PE tubing and implanted subcutaneously behind the neck of the rats. Saline was the vehicle for the systemic drug administration and aCSF was the vehicle for the local infusions. The vehicles were used for the control infusions. The local infusions of nicotine into the mediodorsal thalami nucleus were included to model the effects of chronic nicotinic receptor loss in this area. Chronic systemic nicotine was included in the design because the large majority of people with schizophrenia smoke tobacco and we wanted to determine possible interactions of this drug taking with local nicotinic receptor antagonist infusion and systemic clozapine effects on memory. The infusions lasted four weeks. For the first week of infusion after surgery the rats were given time for recovery and thus were not tested. During the following three weeks the rats were tested three times/week with s.c. injections of clozapine (0, 1.25 and 2.5 mg/kg in a volume of 1 ml/kg) being given in a counterbalanced order. Clozapine was included as a benchmark atypical antipsychotic drug quite effective in the treatment of schizophrenia. The doses used have been previously shown in our studies to span the effect range from being near threshold to being clearly effective in causing memory impairments and sedative effects in the radial-arm maze [22,23,33,34]. Saline was the vehicle and served as the control injection. Injections were administered 20 min before testing on the radial-arm maze in a volume of 1 ml/kg.

2.6. Histology

Following the completion of all drug treatments, the rats were killed and the cannula placements were determined. The rats were deeply anesthetized with pentobarbital, killed by exsanguination and perfused with a 9% phosphate buffered saline solution followed by a 4% formaldehyde solution. The brain was removed and stored in 4% formaldehyde. The brain was later frozen on dry ice and sliced with a cryostat in 20 μm sections. Histological slides were made and examined to confirm appropriate cannula placement. Only those subjects with both cannula placements within the mediodorsal thalamic nucleus target area (Fig. 1) were included in the data analysis.

2.7. Statistics

Analysis of variance was performed with working memory errors, reference memory errors and response latency. The acute study had a within subjects repeated measures counterbalanced design in which all of the subjects were given all of the treatments. The chronic study had a mixed design of between subjects factors (local nicotinic antagonist infusion and systemic nicotine infusion) and repeated measures (acute clozapine injections). Planned comparisons were made of the treatments to the control conditions. As recommended by classic statistical text Snedecor and Cochran [35] tests of simple main effects of drug treatments were made after the finding of higher order interactions with $p < 0.10$. The final threshold for all drug effects was $p < 0.05$ (two-tailed).

3. Results

3.1. Study 1: acute nicotinic antagonist effects

Acute doses of MLA and DHβE were locally infused bilaterally into the mediodorsal thalamic nucleus in a repeated measures

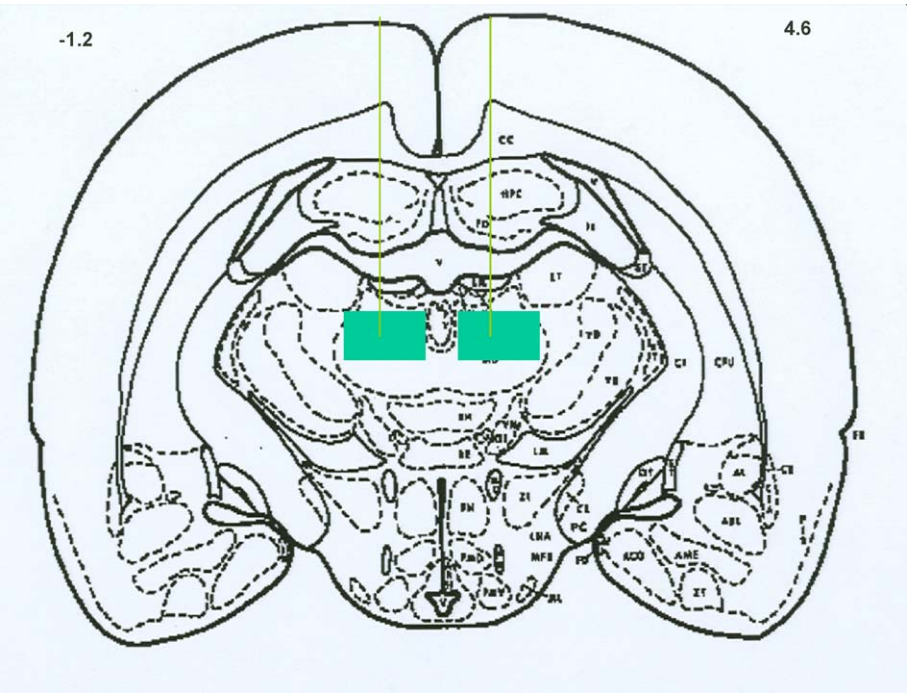

Fig. 1. Location of the local infusions into the mediodorsal (MD) thalamic nucleus [32].

counterbalanced design with all of the subjects receiving all of the treatments. Statistical significance with this within subjects design depended on the consistency of the drug-induced changes. The width of the standard error bars in the figures is an indication of the variance of all of the subjects but not the consistency of the drug effects in changing behavior. In the overall analysis of working and reference errors there was a three-way interaction of MLA × DHβE × error type ($F(3, 51) = 2.53$, $p < 0.10$) that as recommended by Snedecor and Cochran [35] prompted the analysis of MLA × DHβE within each error type (working and reference memory). As shown in Fig. 2, the 6.75 μg/side DHβE dose significantly ($F(1, 51) = 13.49$, $p < 0.001$) improved working memory performance by reducing errors per session. Lower doses of DHβE given by themselves did not significantly alter working memory performance. Interestingly co-administration of 6.75 μg/side of MLA with 6.75 μg/side of DHβE significantly ($F(1, 51) = 22.28$, $p < 0.0001$) reversed the memory improving effect of DHβE. When given by itself 6.75 μg/side of MLA did not significantly affect performance relative to vehicle control. The combinations of MLA at 6.75 μg/side with 1.18 ($p < 0.05$), 3.38 ($p < 0.05$) and 6.75 μg/side ($p < 0.05$) of DHβE slightly but significantly impaired working memory performance relative to MLA alone. But there was no impairment relative to vehicle control.

The DHβE and MLA effects were specific to working memory. As shown in Fig. 3, no significant effect was seen with reference memory errors. Also no significant effects were seen with regard to response latency (data not shown).

3.2. Study 2: chronic nicotinic antagonist effects

Effects on memory of chronic local infusions of the α4β2 nicotinic receptor antagonist DHβE and the α7 antagonist MLA into the mediodorsal thalamic nucleus for four weeks were studied. Each local infusion group, aCSF controls, DHβE and MLA-treated had subjects concurrently infused systemically (s.c.) with nicotine (5 mg/kg/day) or saline as a control. All of the rats were administered acute doses of the antipsychotic drug clozapine in a repeated measures counterbalanced design. With working memory there was a significant nicotinic antagonist × nicotine interaction ($F(2, 83) = 4.13$, $p < 0.025$). Fig. 4 shows the nicotinic antagonist and nicotine interaction averaged over the acute clozapine doses. Follow-up tests compared individual nicotinic antagonist and nicotine treatment groups. Chronic DHβE infusion into the MD thalamic nucleus with no systemic nicotine caused a significant ($p < 0.05$) improvement in working memory performance of rats vs. those with aCSF infusions and no systemic nicotine treatment. Interestingly, the addition of systemic nicotine treatment to subjects given local DHβE infusions significantly ($p < 0.025$) reversed the improvement. No significant effects of the MLA treatment on working memory were seen (Fig. 4). In this study no significant effects of acute clozapine treatment were seen in the dose range of 1.25–2.5 mg/kg (Fig. 5).

With reference memory there was a significant ($F(2, 82) = 4.89$, $p < 0.01$) main effect of nicotinic antagonist treatment. However, neither treatment significantly differed from the aCSF control as displayed in Fig. 6, which shows the nicotinic antagonist and nicotine interaction averaged over the acute clozapine doses and

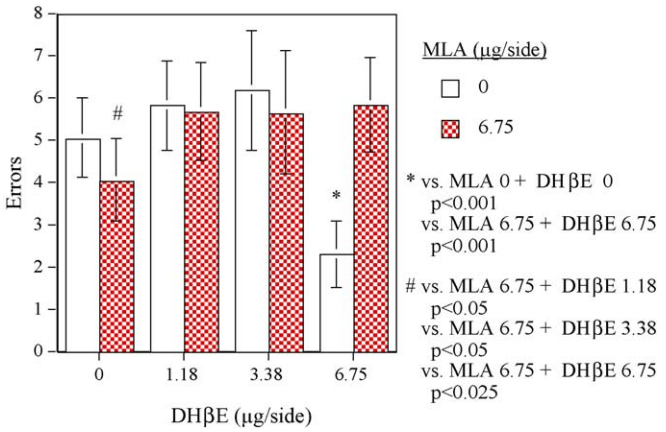

Fig. 2. Working memory errors after acute local infusions of MLA and DHβE into the mediodorsal thalamic nucleus (mean ± SEM).

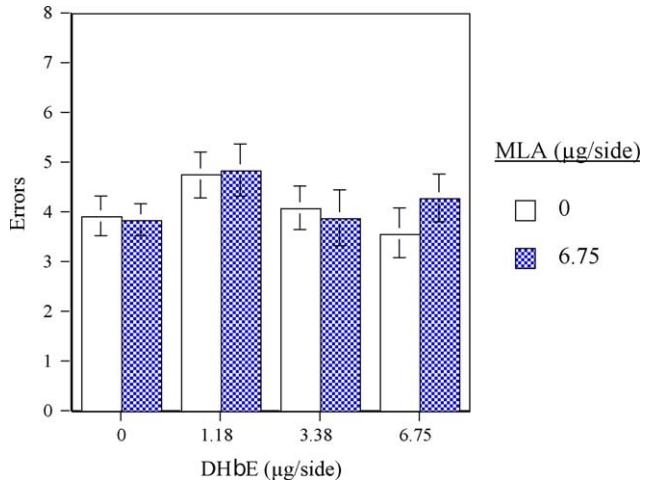

Fig. 3. Reference memory errors after acute local infusions of MLA and DHβE into the mediodorsal thalamic nucleus (mean ± SEM).

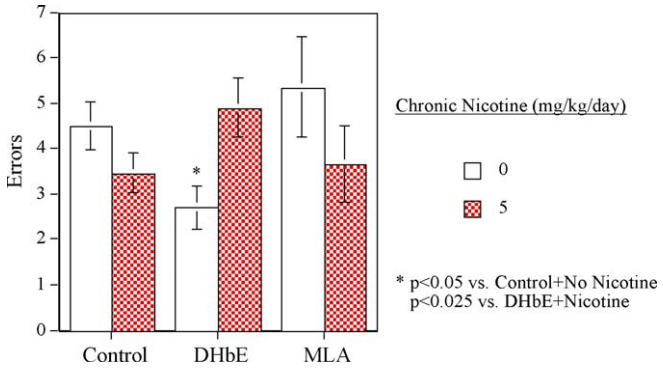

Fig. 4. Working memory errors after chronic local infusions of MLA and DHβE into the mediodorsal thalamic nucleus (mean ± SEM) with the nicotinic antagonist and nicotine interaction averaged over the acute clozapine doses.

Fig. 7 which shows the more detailed data for each clozapine dose. There was a significant ($F(2, 166) = 5.12$, $p < 0.01$) main effect of clozapine. The 2.5 mg/kg clozapine dose significantly ($p < 0.005$) lowered the number of reference memory errors from an average of 4.13 ± 0.18 after acute saline injections to 3.55 ± 0.14 after 2.5 mg/kg clozapine. The lower 1.25 mg/kg clozapine dose did not significantly affect reference memory error rate (3.92 ± 0.16).

Response latency was not significantly affected by nicotine or nicotinic antagonist administration (Fig. 8). Clozapine caused a

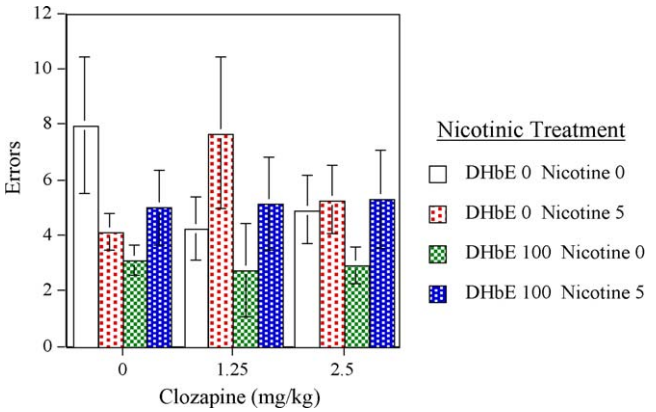

Fig. 5. Working memory errors after chronic local infusions of MLA and DHβE into the mediodorsal thalamic nucleus (mean ± SEM) with the local nicotinic antagonist infusions, chronic systemic nicotine and the acute clozapine doses.

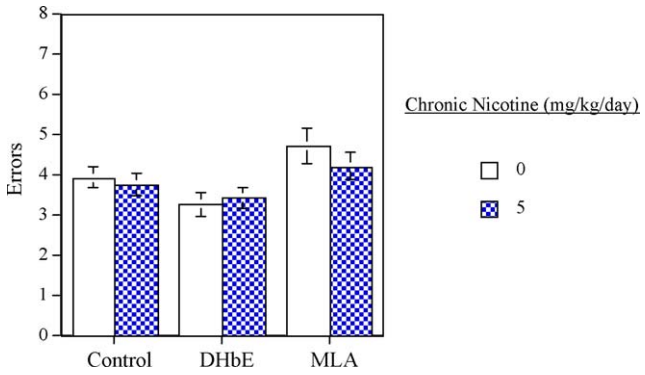

Fig. 6. Reference memory errors after chronic local infusions of MLA and DHβE into the mediodorsal thalamic nucleus (mean ± SEM) with the nicotinic antagonist and nicotine interaction averaged over the acute clozapine doses.

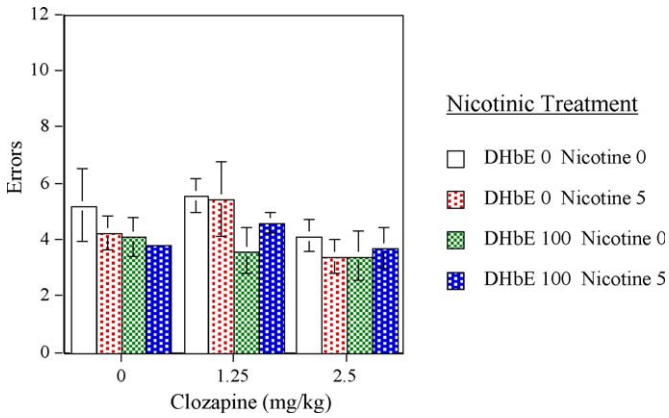

Fig. 7. Reference memory errors after chronic local infusions of MLA and DHβE into the mediodorsal thalamic nucleus (mean ± SEM) with the local nicotinic antagonist infusions, chronic systemic nicotine and the acute clozapine doses.

significant ($F(2, 166) = 19.66$, $p < 0.0005$) sedative effect, with the higher (36.9 ± 4.4 s per entry), but not the lower clozapine dose (20.9 ± 1.1) causing significant ($p < 0.0005$) slowing of response compared with controls (13.0 ± 0.6).

4. Discussion

Regional heterogeneity is pronounced for the functional importance of nicotinic receptors for cognitive function. It is clear that blockade of nicotinic receptors in some areas such as the hippocampus and amygdala impairs working memory function

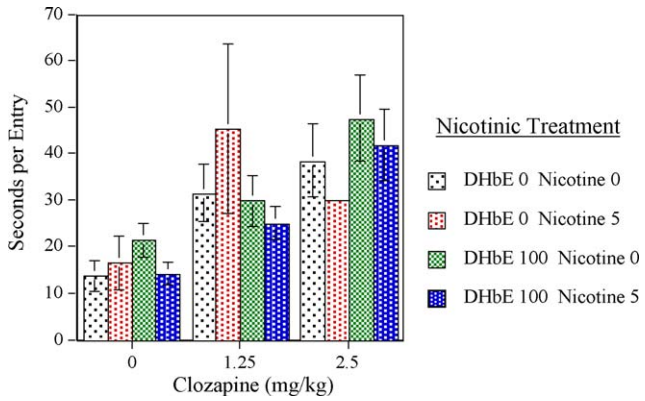

Fig. 8. Response latency after chronic local infusions of MLA and DHβE into the mediodorsal thalamic nucleus (mean ± SEM) with the local nicotinic antagonist infusions, chronic systemic nicotine and the acute clozapine doses.

[19,24]. In contrast, the current studies demonstrated that nicotinic receptor blockade in another area, the mediodorsal thalamic nucleus, can improve working memory function. This brain regional heterogeneity of function is important for the development of effective nicotinic-based therapeutics for cognitive impairment.

In the current studies, both the acute and chronic local infusions of the α4β2 nicotinic antagonist DHβE into the mediodorsal thalamic nucleus significantly improved working memory of rats in the radial-arm maze. This is opposite of the effect of memory impairment when these same acute and chronic doses of DHβE are infused into the hippocampus [17–19,21,22,36]. The anatomic location of nicotinic receptors in the brain makes critical difference in the functional effect of drug actions.

The memory improvement caused by an acute dose of DHβE infused into the mediodorsal thalamic nucleus was reversed by co-administration an acute dose of the α7 antagonist MLA that by itself had no significant effect on memory relative to control. MLA also caused slight but significant deficits when given in combination with lower doses of DHβE. Nonadditive effects of α7 and α4β2 antagonists have also been seen with infusions into the ventral hippocampus and basolateral amygdala [19,24]. In the hippocampus both types of antagonists impair working memory, but when given in combination they do not cause a greater memory impairment [19]. This is not due to a ceiling effect on the task, since other manipulations like NMDA receptor blockade are fully able to produce substantially greater memory impairment [37]. In the basolateral amygdala both α7 and α4β2 antagonists can impair working memory, but when given together α7 blockade can reverse impairment caused by α4β2 blockade [24]. These findings together with the current data showing that α7 blockade in the mediodorsal thalamic nucleus counteracts the working memory improvement caused by α4β2 blockade demonstrates the complex and at time mutually antagonist relationships of α7 and α4β2 nicotinic receptors. In terms of drug development, it may be the case that drugs with effects on both receptor subtypes may have diminished efficacy due to multiple receptor effects counteracting each other.

It was interesting that chronic systemic nicotine counteracted the working memory improvement caused by chronic DHβE infusion into the mediodorsal thalamic nucleus. In prior studies with un-operated animals this dose of 5 mg/kg/day of nicotine caused significant memory improvement (for review see Ref. [7]). In the current study, chronic nicotine caused a significant ($p < 0.05$) improvement in the rats with aCSF or MLA infusions in the mediodorsal thalamic nucleus when clozapine was not given as a co-treatment. Previously, we have found that clozapine can block cognitive improvements induced by nicotine [38].

Cognitive improvement caused by nicotinic antagonists has been seen previously [11–13]. We have shown that chronic low dose infusion with the nicotinic antagonist mecamylamine improves working memory performance [11]. And, more recently we have shown that there is a low dose mecamylamine-induced improvement of learning [12].

In the current study we did not find clozapine to significantly impair working memory performance as we had in several previous studies which showed working memory and attentional impairments with clozapine in this dose range [22,33,34,38–41]. It may be the case that modest disruption of mediodorsal thalamic nucleus neurons with the local infusion procedure altered the clozapine effects on working memory. The sedative effects of clozapine were however, the same in the current study as it has been in all the earlier studies.

Why is it important to discover the regional heterogeneity of nicotinic involvement in cognitive function? First, it is vital for an accurate basic understanding of how the brain works in the production of important cognitive functions such as memory. Second, the regional heterogeneity of nicotinic receptor function with regard to memory could help explain the varying nicotinic drug actions in different settings. It may be the case that under differing environmental, behavioral and clinical circumstances, regionally distinct nicotinic systems play more or less predominant roles in overall cognitive function. Third, it may provide an explanation of individual and group differences in response to nicotine and other nicotinic drugs. Between individuals there may be key differences in which different areas are predominantly used for the function of memory. Accurate indexing of the regionally specific activity of nicotinic receptor actions during memory performance could help determine which type of treatment would be most useful for improving memory.

These studies consistently show that DHβE infused into the mediodorsal thalamic nucleus significantly improves working memory performance, implying that decreased α4β2 nicotinic receptor activity in this area improves memory. Inasmuch as the very same acute and chronic doses of DHβE in other areas such as the hippocampus significantly impair working memory performance in the same task demonstrates that location of nicotinic receptors is vitally important to the valence of their effect on memory. Given that drug treatments are given systemically they go to all areas of the brain. The heterogeneity of action of regionally diverse nicotinic receptors poses a quandary for therapeutic drug development. The brain did not evolve for the convenience of pharmaceutical activity. Systemically administered drugs bathe the brain in a hormone-like fashion, whereas the brain is made up of many interconnected regions, which play diverse roles in the neural bases of behavioral function. How can neuropharmaceutical development address the fact that the same receptor subtypes in different areas of the brain play different roles in behavioral function? The current appreciation of nicotinic receptor classes rely on the pentameric structure of the core receptor, but it may be the case that future discoveries will permit more accurate discernment of differences among receptors based on ancillary modulating processes. Thus, α4β2 receptors in one area like the hippocampus which when blocked impair memory may be different in some ancillary manner from α4β2 receptors in another area like the mediodorsal thalamic nucleus which when blocked improve memory. The discovery of the differential roles of nicotinic receptors in various parts of the brain for memory could help direct the search for subtypes of subtypes of nicotinic receptors such that more specific drugs could be developed to improve memory.

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