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Interaction of nicotinic and histamine H₃ systems in the radial-arm maze repeated acquisition task

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Abstract

Nicotinic systems have been found in a variety of studies to play important roles in cognitive function. Nicotinic involvement in different aspects of cognitive function such as learning vs. memory may differ. We have found in rats that the spatial repeated acquisition task in the radial-arm maze is significantly improved by low doses of the nicotinic receptor antagonist mecamylamine, the atypical nicotinic receptor ligand lobeline, as well as the $\alpha 7$ nicotinic receptor agonist ARR-17779. Interestingly, nicotine in the same dose range that improves working memory in the win-shift radial maze task was not effective in improving repeated acquisition performance. Nicotinic systems interact with a variety of other neural systems. Differential involvement of these extended effects with learning vs. memory may help explain differential effects of nicotinic drugs with these cognitive functions. Histamine H₃ receptor antagonists have been shown by some studies to improve cognitive function, but others have not found this effect and some have found impairment. Nicotine stimulates the release of histamine. This effect may counter other cascading effects of nicotine in the performance of learning and memory tasks. A specific test of this hypothesis involves our study of nicotine (0.1-0.4 mg/kg) interactions with the histamine H₃ receptor antagonist thioperamide (2.5-10 mg/kg) on learning memory in the repeated acquisition test in the radial-arm maze. The highest dose of thioperamide tested caused a significant choice accuracy impairment, which was most evident during the later portions of the learning curve. The highest dose of nicotine did not change overall errors but did cause a significant impairment in learning over trials. The choice accuracy impairment induced by thioperamide was significantly attenuated by nicotine (0.4 mg/kg). The learning impairment caused by the highest dose of nicotine was significantly attenuated by thioperamide. Thioperamide also caused a slowing of response, an effect, which was attenuated by nicotine coadministration. The repeated acquisition test can help differentiate acute drug effects on learning. Nicotine and thioperamide effectively reversed each other's choice accuracy impairment even though each by itself impaired accuracy.

Keywords

nicotine; histamine; H₃; thioperamide; repeated acquisition; radial-arm maze

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1. Introduction

Nicotine has been found in many studies to improve cognitive function, although other studies have not found improvements and some have found impairments (Levin, 1999;2000a;Levin et al., 2006;Levin et al., 2004;Puma et al., 1999;Rezvani and Levin, 2001;Stolerman et al., 1995;Yilmaz et al., 1997). Some of the differences in findings appear to be due to the type of cognitive function under study. Memory and attentional function have been generally found to be improved by nicotine treatment, however nicotine effects on learning have been more equivocal. For example, in the radial-arm maze, the same nicotine dose range that improves working memory performance (Levin et al., 2006) does not improve or slightly impairs repeated acquisition (Levin and Christopher, 2003;Levin and Caldwell, 2006). Interestingly, selective $\alpha 7$ nicotinic stimulation with ARR-17779 (Levin et al., 1999), low-dose nicotinic blockade with mecamylamine (Levin and Caldwell, 2006) or the atypical nicotinic ligand lobeline (Levin and Christopher, 2003) have been found to significantly improve repeated acquisition in the radial-arm maze. The specific neurochemical actions of nicotinic ligands may also help to explain cognitive effect of nicotinic treatment.

Nicotinic systems interact with a variety of other neurotransmitter systems with regard to cognitive function (Decker and McGaugh, 1991;Levin et al., 2006). Nicotine has a variety of effects mediated through its facilitation of the release of a variety of different neurotransmitters including dopamine, norepinephrine, serotonin, acetylcholine, GABA, glutamate and histamine (Wonnacott et al., 1989). It is possible that only some portions of nicotine effects are effective in improving learning, while other aspects impair learning. In a series of studies we have examined the interaction of nicotinic effects with a variety of other neurotransmitter systems (Levin et al., 2006).

Histamine is an interesting candidate for important interactions with nicotinic systems with regard to cognitive function given the demonstration of histaminergic drug effects on cognitive performance. Nicotinic and histaminergic systems appear to play complementary roles in cognitive function (Blandina et al., 2004). Histamine coadministration was found to reduce the improvement in passive avoidance learning by nicotine, whereas histamine H_1 receptor antagonists enhanced nicotine-induced improvements (Eidi et al., 2003). Histamine stimulates the activity of cholinergic cells in the septum and basal forebrain, but the interaction of histaminergic and nicotinic systems likely differ substantially according to the receptor subtypes involved (Bacciottini et al., 2001). The histamine H_3 receptor acts as a presynaptic autoreceptor that inhibits histamine release from histaminergic neurons in the brain (Arrang et al., 1983). Thioperamide like other H_3 antagonists stimulates the release of histamine (Prast et al., 1994). Histamine H_3 receptor expression is not confined to histaminergic neurons, and, as a heteroreceptor, the histamine H_3 receptor is known to modulate various neurotransmitter systems in the brain. In rodent and/or human brains, histamine H_3 receptor activation inhibits presynaptically the release of many important neurotransmitters (Leurs et al., 2000). It may be the case that enhancing histamine release caused by nicotine may help or hinder nicotinic actions on learning function.

The current study was conducted to determine the interactions of nicotinic and histamine H_3 receptor systems with regard to choice accuracy and learning function as measured by the repeated acquisition test on the radial-arm maze. Histaminergic H_3 antagonists have been found to significantly improve memory function. The effects on learning and interactions with nicotinic effects have been to date unstudied. The current study determined the effects of H_3 antagonism on learning in the radial-arm maze as well as its interaction with nicotine actions.

2. Materials and Methods

2.1. Subjects

Young adult (2-4 months old) female Sprague-Dawley rats (Taconic Farms, Gemantown, NY, USA) were used (N=12). The rats were housed in plastic cages on a reverse 12-h light/12-h dark cycle to facilitate behavioral testing during the dark phase when they were active. The rats had *ad libitum* access to water and were fed daily (%80 of their free access intake) after testing to keep them at a lean and healthy (normally active) weight and motivated for the food reinforcements used in the learning task. The average weights for the female rats in this study averaged approximately 280 g. These studies were conducted under an approved protocol of the Animal Care and Use Committee of Duke University.

2.2 Repeated Acquisition Training

Repeated acquisition testing is quite useful for differentiating drug effects on learning *per se* vs. non-learning aspects of cognitive function. Since the rats are naïve on trial 1 of each session, their choice accuracy within that trial would be influenced by several different cognitive processes including attention, memory of choices within the trial and motivation. The learning would then be the improvement of accuracy over the succeeding trials of a session. Thus, the repeated acquisition task can index learning vs. non-learning aspects of performance.

Radial arm-maze choice accuracy has been found to be stable across the estrous cycle in female rats (Stackman et al., 1996). The eight-arm maze is a standard test and a sensitive measure of learning and working memory performance (Levin, 2000b).

An automated radial-arm maze (Med Associates Inc., Georgia, VT, USA) was used. The rats were trained on an automated 8-arm radial maze elevated 5 cm from the floor with a central platform of 30 cm in diameter and 32.5 cm height from which extend the arms with the dimensions of 17.5 × 12.5 × 67.5 cm. Clear Plexiglas walls are at the sides and on the top of each arm. Each arm is separated from the central platform by vertical aluminum gates. Feeders are located at the end of each arm and feed one pellet (P.J. Noyes Co Inc.) at a time. The maze was in a room, which contained extra-maze visual cues that were always kept in the same position when testing. The rats were first handled for 5 min for few days to accustom them to human contact. They were then shaped by being placed in the center of the maze with 15 pellets and kept there until all the pieces had been eaten or a maximum of 15 min had ended. Once the rats had consumed the food reinforcers within the 15 min allocated, training on the maze was started. This involved baiting 3 of the 8 arms with reinforcers. The same 3 arms were kept baited for an individual rat for 5 continuous trials in which they chose arms until they had selected the three baited arms or a maximum of 3 min. Then the next trial was immediately started with the return of the rat to the center of the maze and after 10 seconds the doors to the arms were opened. Different random combinations of arms were baited in different sessions. Not more than two adjacent arms would be baited. To start the session, the rat was placed in the central cylinder and program would start after 10s. The gates open making rats free to move around the maze for 3 min or until all baited arms were chosen. An entry was considered as entrance to the arm and walking to the end. Entries to any arms other than the first time entry to the baited arms were counted as errors. The dependent measure for repeated acquisition was errors per trial on trials 1 in which the rat was naïve to the arms that were rewarded for that particular session and errors on trials 2-3 and 4-5 during which learning was expressed. The response latency measure was the total trial duration divided by the total number of arm entries (seconds per entry). Data from a trial were included in analysis if all three of the baited arms were selected within the 180 second time limit. If only two baited arms were selected, an error of omission was added to the error score for that trial. If only one or no baited arms were selected within the 180 second time limit then the error data were not included in the analysis.

The rats were trained on the maze at least twice weekly until reach a stable level of performance before drug administration was carried out.

2.3. Drug Administration

The rats were injected (s.c.) with nicotine hydrogen tartrate salt (Sigma-Aldrich Inc., St. Louis, MO, USA) (0, 0.1, 0.2 and 0.4 mg/kg) which was injected alone or in combination with the histamine H₃ receptor antagonist thioperamide (Sigma-Aldrich Inc., St. Louis, MO, USA) (0, 2.5, 5 and 10 mg/kg) in a repeated measures counterbalanced design in a volume of 1 mg/kg 20 minutes before the onset of testing with at least two days between drug doses. Rats were not trained on the days between drug sessions.

2.4. Statistical Analysis

The choice accuracy data (errors) and latency data (seconds/entry) were assessed for statistical significance by analysis of variance with the threshold for significance set at $P < 0.05$ (two-tailed) for all analyses. A three-way analysis within nicotine dose level (0, 0.1, 0.2 and 0.4 mg/kg), thioperamide dose level (0, 2.5, 5 and 10 mg/kg) and session trial block (trial 1, 2-3, and 4-5) as factors.

3. Results

Thioperamide, a histamine H₃ receptor antagonist, caused a choice accuracy impairment with the high dose of 10 mg/kg causing a significant ($F(1,33)=4.59$, $P < 0.05$) increase in errors averaged over the course of the session (Fig. 1). There was a significant main effect of ($F(2,22)=25.89$, $P < 0.0001$) improvement in choice accuracy over the course of the session. The interaction of drug dose and trial block was not significant so no firm statements can be made concerning differential effects of thioperamide on different phases of the session, although as can be seen in figure 1 there is no indication of an increase in errors with 10 mg/kg thioperamide during the initial trial.

The thioperamide-induced impairment was reversed by nicotine co-treatment. This effect was reversed by nicotine co-treatment with the high dose of nicotine (0.4 mg/kg) significantly ($F(1,33)=5.67$, $P < 0.05$) attenuated the choice accuracy impairment caused by thioperamide (Fig. 2). Nicotine had this effect even though when given by itself it did not improve choice accuracy. In fact, with the 0.4 mg/kg nicotine dose there was not significant learning over the repeated acquisition session (Fig. 3, upper left panel), as there was with saline ($P < 0.01$) or the lower nicotine doses of 0.1 mg/kg ($P < 0.005$) and 0.2 mg/kg ($P < 0.025$). In analyzing the linear trend of choice accuracy improvement over the five trials of the session the 0.4 mg/kg nicotine dose caused a significant decline relative to the vehicle control condition ($F(1,99)=6.33$, $P < 0.025$). This learning impairment was significantly reversed by the 5 mg/kg dose of thioperamide ($F(1,99)=6.21$, $P < 0.025$). The higher (10 mg/kg) and lower (2.5 mg/kg) thioperamide doses were not as effective, providing no significant improvement in learning rate.

Response latency was also affected by thioperamide and nicotine. The 10 mg/kg thioperamide dose significantly ($P < 0.05$) increased response latency (Fig. 4). Nicotine by itself significantly decreased response latency at the 0.2 mg/kg ($P < 0.05$) and 0.4 mg/kg ($P < 0.005$) doses. Nicotine significantly ($P < 0.0001$) reversed the thioperamide-induced slowing of response.

4. Discussion

The histamine H₃ receptor antagonist thioperamide caused a significant impairment in choice accuracy in the radial-arm maze repeated acquisition procedure. When the rats were given the 10 mg/kg thioperamide dose they showed choice accuracy impairment relative to vehicle

control treatment. There was not a significant thioperamide $\times$ trial effect so no rigorous statements can be made concerning differential thioperamide effects across trials. However, it is clear from figure 1 that there were not increased errors caused by thioperamide treatment in the first trial.

The complex effects seen in the literature may be due to differential involvement of histamine H₃ receptor systems in various aspects of cognitive function. The repeated acquisition task can differentiate effects on learning (improvement across trials) vs other aspects of cognitive function such as attention and memory (effects present throughout the session). The current finding is that thioperamide significantly impaired the improvement over trials within a session indicating an impairment in learning aspects of the repeated acquisition task. Nicotine significantly attenuated the thioperamide-induced impairment even though by itself it decreased improvement over trials

The interactive effects of nicotine and thioperamide showed that the slowing of response caused by the highest thioperamide dose was counteracted by nicotine, which by itself reduced latency. Response latency on the radial-arm maze is orthogonal to choice accuracy. Increases or decreases in latency *per se* have not been found to be related to accuracy. This measure was included for completeness of behavioral assessment and to provide information about the extent of interactions of nicotine and thioperamide. Response latency represents an ancillary behavioral measure, which provides an indication of the generality of the pharmacological effects. In the current case it appears the nicotine provides a more general attenuation of thioperamide effects than only reversal of choice accuracy impairment.

Although there is evidence that pharmacological blockade of histamine H₃ receptors improves cognitive function (Fox et al., 2002; Fox et al., 2003; Giovannini et al., 1999; Ligneau et al., 1998; Meguro et al., 1995; Prast et al., 1996), but the overall picture of the cognitive effects induced by compounds changing the activity of brain histamine remain contradictory (Brown et al., 2001; Chen et al., 1999; Sakai et al., 1998; Tasaka et al., 1985). Histaminergic H₃ receptor activation, for instance, modulates acetylcholine release and cognitive processes, apparently with modalities that differ according to their role as autoreceptors (Blandina et al., 1996; Cangioli et al., 2002; Passani et al., 2001). The current study used the repeated acquisition task, which focuses on measuring new learning. The H₃ antagonist induced impairment on this task points to the specificity of the involvement of H₃ systems in cognitive function.

There are studies reporting facilitation and others an impairment of the acquisition of conditioned avoidance responses or aversively-motivated maze tasks in rats treated prior to trials with intracerebroventricular (ICV) histamine or systemic injections of the histamine synthesis precursor l-histidine (Cacabelos and Alvarez, 1991; Tasaka et al., 1985). Similarly, a decrease in brain histamine, induced by systemic or ICV injections of the inhibitor of neuronal synthesis of histamine alpha-fluoromethylhistidine (alpha-FMH) can also induce a facilitation (Cacabelos and Alvarez, 1991; Sakai et al., 1998) or an impairment (Chen et al., 1999; Kamei et al., 1993) of the acquisition of these responses in rats.

The precise timing of drug effects on histamine receptor actions and the distinct actions of different histaminic receptor subtypes may contribute to the complex cognitive effects of these manipulations. The architectural constraints that separate groups of transmitters in particular brain structures, and the nature of the cognitive task used likely also contribute to whether histamine has facilitatory or inhibitory effects.

Similar to our study, histamine H₃ receptor antagonists impair contextual fear conditioning (Passani et al., 2001). Local perfusion with either histamine H₃ receptor antagonists or histamine H₃ receptor agonists, at concentrations comparable with those that affected fear memory in the behavioral experiments, decrease (Passani et al., 2001) or increase (Cangioli et

al., 2002) acetylcholine release from the basolateral amygdala (BLA), respectively. In the BLA, histamine H₃ receptor binding is strictly associated with the presence of histaminergic fibers (Anichtchik et al., 2000), and local perfusion with histamine H₃ receptor antagonists increases endogenous histamine release (Cenni et al., 2004); therefore, the inhibition of acetylcholine release elicited by histamine H₃ receptor antagonists could be most simply explained by a blockade of histamine H₃ autoreceptors dominant to histamine H₃ heteroreceptors. Such deficit in acetylcholine might be involved in how nicotine attenuates the cognitive impairing effects of histamine H₃ receptor antagonist in our study. Similar to our observation of decreased response latency by nicotine, in another study Nicotine increased the number of trials completed in the 5-choice serial reaction time task (Bizzaro and Stolerman, 2003).

Functional receptor isoforms of the histamine H₃ receptor display different pharmacological profiles (Wellendorph et al., 2002), and are distributed in the central nervous system in a heterogeneous fashion (Drutel et al., 2001). Thus, research with more selective receptor agonists and antagonists for the histamine H₃ receptor, as well as ligands for its various isoforms, according to receptor subtypes aimed on particular brain region of interest is suggested.

In conclusion we have shown thioperamide caused a significant impairment on repeated acquisition choice accuracy especially during the mid to late portions of the acquisition curve. The thioperamide-induced impairment was reversed by nicotine treatment. Nicotine given alone did not improve choice accuracy. In fact, with high dose (0.4 mg/kg) of nicotine, there was not significant learning over the repeated acquisition session. Response latency was also affected by thioperamide and nicotine. Thioperamide significantly increased response latency. Nicotine by itself significantly decreased response latency. Nicotine in any of its doses significantly reversed the thioperamide-induced slowing of response.

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Figure 1.

Thioperamide-induced impairment in choice accuracy compared with performance of the rats after the saline vehicle injection condition in the experiment the across the learning curve (mean $\pm$ sem).

H3-Nicotinic Interactions: Choice Accuracy in Repeated Acquisition

Figure 2.

Nicotine-induced attenuation of the choice accuracy impairment caused by thioperamide compared with performance of the rats after the saline vehicle injection condition in the experiment Error: Average of errors (from trials, 1, 2-3 and 4-5, mean±sem).

Nicotine-Thioperamide Interactions across Trials

Figure 3.

Nicotine-induced attenuation of learning in the radial-arm maze (mean±sem) compared with performance of the rats after the saline vehicle injection condition in the experiment.

H3-Nicotinic Interactions: Response Latency in Repeated Acquisition

Figure 4. Nicotine-induced speeding of response and reversal of the slowing caused by thioperamide (mean±sem) compared with performance of the rats after the saline vehicle injection condition in the experiment.