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Evaluation of muscarinic and nicotinic receptor antagonists on attention and working memory

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Abstract

Cholinergic receptor antagonists are commonly used to model attentional and mnemonic impairments associated with neuropsychiatric disorders such as Alzheimer's disease. However, few studies have systematically assessed the effects of these drugs following manipulations that affect attention or working memory within the same task. In the present experiment, rats were trained to discriminate visual signals from "blank" trials when no signal was presented. This task was modified to include retention intervals on some trials to tax working memory. During standard task performance, rats received systemic injections of the muscarinic receptor antagonist, scopolamine, or of the nicotinic receptor antagonist, mecamylamine. A second experiment tested the effects on this task of co-administering doses of scopolamine and mecamylamine that, when administered alone, did not significantly affect task performance. Scopolamine (0.3 and 1.0 mg/kg) decreased detection of 500 ms signals but did not affect accurate identification of non-signals. Scopolamine did not differentially affect performance across the retention interval. Elevated omission rates were associated with high doses of scopolamine or mecamylamine. Combination drug treatment was associated with decreased signal detection and elevated omission rates. Collectively, the data suggest that muscarinic and nicotinic receptor antagonists do not exclusively impair working memory.

Keywords: Acetylcholine; Attention; Cholinergic; Mecamylamine; Rat; Scopolamine; Vigilance; Working memory

1. Introduction

Cholinergic neurons projecting to widespread areas of the cortex largely originate within the substantia innominata and nucleus basalis of Meynert (Baskerville et al., 1993; Eckstein et al., 1988; Grove, 1988; Lamour et al., 1984; Mechawar et al., 2000; Mesulam, 1995, 2004; Mesulam et al., 1983). A series of studies employing excitotoxic (Muir et al., 1994; Robbins et al., 1989) and, more recently, immunotoxic lesions (Chiba et al., 1999; McGaughy et al., 1996, 2000, 2002) have generally supported the idea that the basal forebrain corticopetal cholinergic system contributes to aspects of attention, but seems to play a more minor role in mnemonic processing (Everitt and Robbins, 1997; Sarter et al., 2005). However, it has recently been suggested that this system may play a more critical role in working memory when attentional demands are taxed (Sarter et al., 2003).

The use of muscarinic and nicotinic receptor ligands to study the role of cholinergic receptor subtypes in attention and working memory has been extensive. Experiments have suggested that muscarinic receptor blockade disrupts performance in measures of attention and working memory (Chen et al., 2004; Herremans et al., 1995; LeBlond et al., 2002; Maviel and Durkin, 2003; Mirza and Stolerman, 2000; Mishima et al., 2002; Power et al., 2003; Robinson, 1997; Roitblat et al., 1989; Ruotsalainen et al., 2000). Nicotine appears to enhance attention, at least under some circumstances, most commonly following pre-exposure to the drug (Hahn et al., 2002; Hahn and Stolerman, 2002) while nicotinic receptor antagonists impair attention (Rezvani et al., 2002; Turchi et al., 1995; but see Mirza and Stolerman, 2000). Other studies have suggested that nicotine is more critically involved in aspects of working memory (Levin and Simon, 1998). Several different behavioral assays have been used to assess

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attention and working memory in these experiments. One challenge in comparing the results from these studies is that the experimental paradigms vary along a number of dimensions including complexity of the task rules, deprivation and reinforcement schedules, and motoric demands. To clarify the roles of these systems in attention and working memory, it may be beneficial to use a single task that allows manipulations of attentional and working memory demands. Furthermore, modifying well-established behavioral assays for attention to include a working memory requirement would allow the assessment of the effects of challenges to the cholinergic system on working memory during an attention-demanding task. One measure of attention commonly employed with rodents, the five choice serial reaction time task, has been successfully manipulated for this purpose (Chudasama et al., 2004; Chudasama and Robbins, 2004; Robbins, 2002).

Another task that has been employed to assess attention is a two-lever task requiring discrimination of a brief visual signal from "blank" trials when no signal is presented. This task was originally described by Bushnell et al. (1994), and further developed and validated by McGaughy and Sarter (1995) based on a taxonomy by Parasuraman et al. (1987). The effects of including a retention interval into this task to tax working memory demands have been described (Burk, 2004). Furthermore, the retention interval is varied from 1–10 s within a session, allowing a comparison of within-session performance during conditions similar to the attention task used by McGaughy and Sarter (1995) (when the retention interval is brief) with performance when the retention interval is increased.

In the present experiment, the effects of systemic administration of the muscarinic receptor antagonist, scopolamine, and the nicotinic receptor antagonist, mecamylamine, were tested in this two-lever attention task with a retention interval. First, a dose-response experiment for both drugs in this task was undertaken. A second experiment tested the effects of co-administration of subthreshold doses (i.e., doses that, when administered alone, did not affect task performance) of scopolamine and mecamylamine to assess whether blockade of both receptor subtypes reveals deficits unobserved at low doses of either drug alone.

2. Method

2.1. Subjects

Subjects were 12 Long-Evans male rats, 2 months old at the start of the experiment (Charles River Laboratories, Inc., Wilmington, MA). These animals were used in a previous experiment that involved several task manipulations but no drug treatment (Burk, 2004). Animals were housed individually in hanging wire cages in a vivarium with a 14/10 h light/dark cycle (lights on 0600–2000). All behavioral testing occurred during the light cycle between 0900 and 1200, for seven days a week. Rats were permitted to feed freely, but were water restricted for the duration of the experiment, receiving water during task performance and for 30 minutes following testing sessions. The experimental protocol was approved by the Institutional Animal Care and Use Committee at the College of William and Mary.

2.2. Apparatus

Rats were trained in eight chambers (Med Associates, Georgia, VT) each enclosed within a sound-attenuating box. One side of the chamber contained two retractable levers, a water port with a dipper to deliver water (0.1 ml) situated between the two levers, and a centrally located panel light located above the water port. A houselight was located in the back of the chamber. The illuminance levels of the panel light and houselight have been previously reported (Burk, 2004). Execution of the behavioral testing programs and data collection were managed by a personal computer utilizing Med-PC version IV software.

2.3. Training procedures

The training procedures and task manipulations that these rats received prior to this experiment have been described previously (Burk, 2004). The houselight remained illuminated throughout all testing sessions. In the first stage of training, the levers were extended throughout the session and the dipper was raised following each lever press with the rule that following five consecutive presses on a single lever, the other lever must be pressed to receive water access. The rule was included to attempt to prevent a lever bias. After reaching a criterion of 120 lever presses per session for three sessions, rats were trained to discriminate between signals (1 s illumination of panel light) and non-signals (no illumination of panel light). After a signal or non-signal, the levers were extended into the chamber. Following a signal, a press on the left lever was the correct choice, scored as a hit, and the dipper was raised. A response on the right lever was considered incorrect and scored as a miss. After a non-signal, a press on the right lever was considered correct, scored as a correct rejection, and water access was given, while depression of the left lever was scored as a false alarm. Failure to press either lever within 3 s was considered an omission. The inter-trial interval (ITI) was variable (12±3 s) during training to prevent the rats from being able to anticipate the beginning of the next trial. Incorrect responses were followed by a correction trial that was identical to the previous trial. Three consecutive incorrect responses triggered a forced trial wherein only the correct lever was extended into the chamber for 90 s. For signal trials, the panel light remained illuminated for the duration of the forced trial. Animals were trained in this version of the task until reaching a criterion of 70% hits and 70% correct rejections for three consecutive sessions. In the next level of training, the signal duration was reduced and varied within each session (500, 100 or 25 ms). Furthermore, the ITI was decreased to 9±3 s and correction and forced trials were eliminated. The sessions lasted for a total of 162 trials (approximately 30 min). Animals were trained to a criterion of 70% hits at the 500 ms signal duration and 70% correct rejections for five consecutive sessions. Once at criterion, the final version of the task was introduced. This final version of the task included a retention interval of variable duration (1, 3, 10 s) after the signal (500, 100, 25 ms) or non-signal. In non-signal trials the retention interval effectively increased the duration of the ITI as no intervening event (panel light illumination) demarcated the start of the retention interval.

Following the retention interval, levers were extended to permit response selection. Animals were trained to a criterion of 60% hits at the 500 ms signal duration averaged across all retention intervals and 70% correct rejections for five consecutive sessions. This level of accuracy is similar to another attentional task, the five-choice serial reaction time task, with a retention interval included (Chudasama and Robbins, 2004). After undergoing several task manipulations (Burk, 2004), rats were trained for at least 10 sessions in the standard version of the task before receiving drug administration in the present experiment. Animals were approximately 8–9 months old when beginning drug administration.

2.4. Procedures for scopolamine and mecamylamine administration

Rats were assigned to one of two groups (scopolamine or mecamylamine administration; $N=6$/group). The first group received systemic injections of scopolamine in doses of 0.05, 0.1, 0.3, 0.5 or 1.0 mg/kg or saline in a counterbalanced order. The second group received systemic injections of mecamylamine in doses of 1.0, 2.0 or 5.0 mg/kg or saline in a counterbalanced order. All injections were administered 30 min prior to the beginning of the session. Rats were trained to re-establish performance levels within 10% of the saline baseline levels at the 500 ms signal and for correct rejections between drug sessions (see Burk and Sarter, 2001 for similar criteria).

As a final treatment, all rats received injections before two additional behavioral testing sessions. Before one of the sessions, rats received injections of 0.05 mg/kg scopolamine and 1.0 mg/kg mecamylamine. During a different session, rats received two saline injections prior to onset of the standard version of the task. The order of these two sessions was counterbalanced across animals. Rats were required to re-establish baseline task performance between the two administration sessions.

2.5. Drug preparation

Scopolamine hydrobromide and mecamylamine hydrochloride (Sigma; St. Louis, MO) were dissolved in 0.9% saline and diluted to appropriate doses prior to injection. Scopolamine is light-sensitive and was stored in an opaque container to prevent degradation. Fresh stock solution was prepared every other day. Excess stock was refrigerated between uses. Each rat was injected intraperitoneally with a volume of 1.0 ml per 1.0 kg of body mass.

2.6. Behavioral measures

The number of hits (h), misses (m), correct rejections (cr) and false alarms (fa) were collected for each session. The relative number of hits was calculated (h/(h+m)) as were the relative number of correct rejections (cr/(cr+fa)). Omissions were recorded but analyzed separately from measures of accuracy.

2.7. Statistical analyses

To normalize the accuracy data, the relative number of hits and correct rejections were angularly transformed ($x' = 2 * \arcsin (x)^{1/2}$; Zar, 1974) and then tested using a repeated measures analysis of variance (ANOVA) with factors including signal duration, retention interval, and dose. For omissions, trial type (signal or non-signal) was included as a factor. The omissions across signal durations were analyzed using a separate ANOVA. The within-subject factor p-values were corrected with the Huynh–Feldt procedure (Maxwell and Delaney, 1990). Significant findings were further analyzed with paired sample t tests. Performance following saline administration was analyzed to test whether rats assigned to receive scopolamine or mecamylamine differed on any measures of performance.

3. Results

3.1. Performance following saline administration

The data from the saline administration session indicated that rats assigned to receive scopolamine or mecamylamine did not

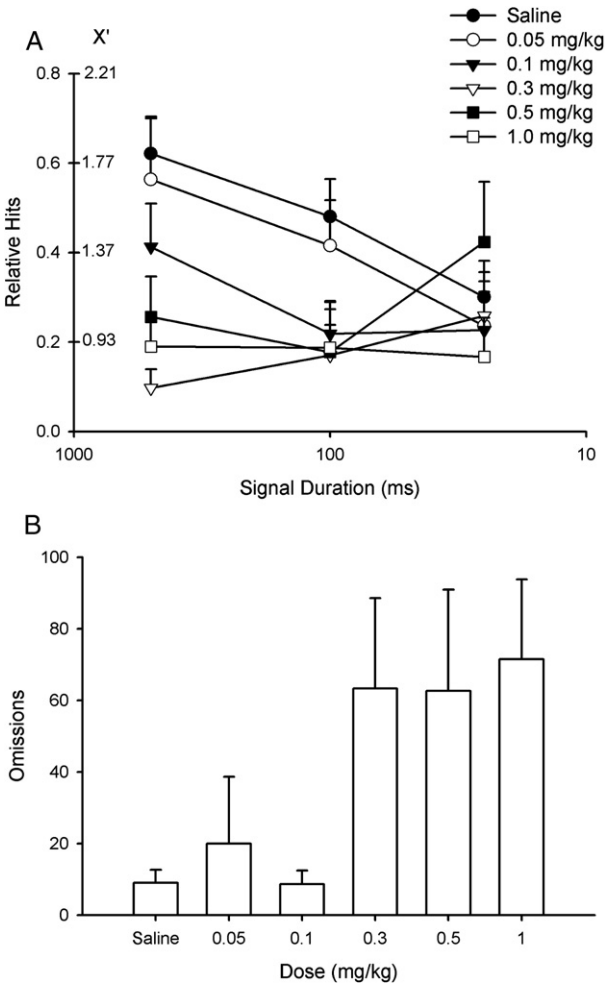

Fig. 1. The top figure (A) represents the relative number of hits (transformed values are presented inside of the axis for comparison) across signal duration following all doses of scopolamine. Generally, the relative number of hits tended to decline as the dose of scopolamine was increased (see Results for details). The bottom figure (B) represents the number of omissions per session (out of 162 total trials) for each dose of scopolamine. Compared to saline, administration of 1.0 mg/kg scopolamine increased the omission rate. Error bars represent SEMs.

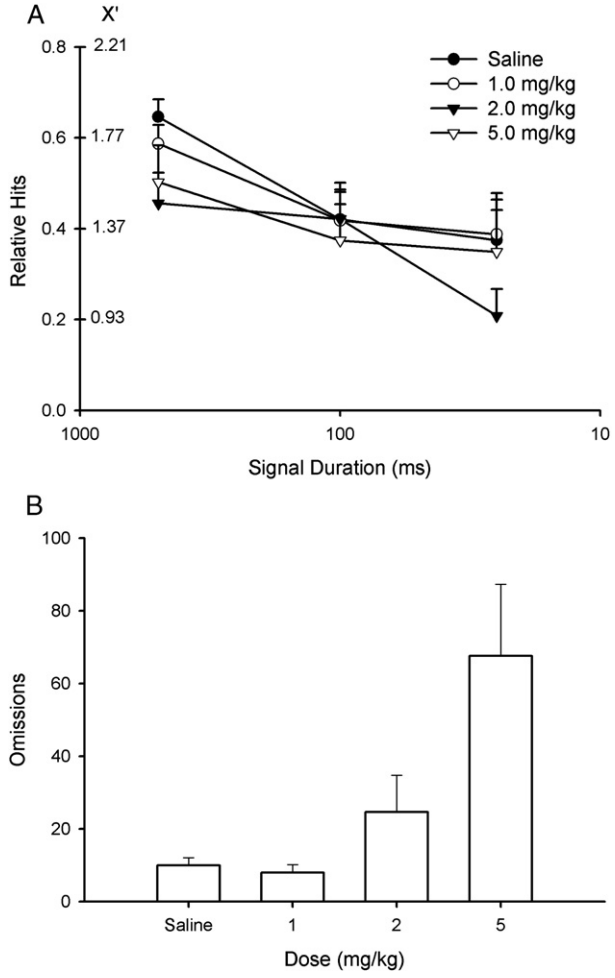

Fig. 2. The top figure (A) represents the relative number of hits (transformed values are presented inside of the axis for comparison) across signal duration following all doses of mecamylamine. Mecamylamine did not significantly affect the hit rate. The bottom figure (B) represents the number of omissions per session (out of 162 total trials) for each dose of mecamylamine. The omission rate increased following 5.0 mg/kg mecamylamine. Error bars represent SEMs.

differ in their hits, correct rejections, or omission rates. For hits, there was a significant main effect of signal duration ($F(2,20)=22.7$, $p<0.001$) and retention interval ($F(2,20)=5.07$, $p=0.024$), reflecting a decrease in accuracy at briefer signal durations and at longer retention intervals. Subsequent analyses demonstrated that, compared with the 500 ms signal, hits were lower to the 100 ms ($t(11)=3.91$, $p=0.002$) and 25 ms signals ($t(11)=6.12$, $p<0.001$) and that hits were lower to the 25 ms signal compared with the 100 ms signal ($t(11)=3.06$, $p=0.011$; relative hits±SEMs: 500 ms: 0.661±0.043; 100 ms: 0.439±0.055; 25 ms: 0.310±0.059). Hits were also lower following a 10 s retention interval compared with a three second retention interval ($t(11)=4.13$, $p=0.002$; relative hits±SEMs: 3 s: 0.552±0.041; 10 s: 0.447±0.049). Consistent with previous findings (Burk, 2004), correct rejections did not vary across retention interval.

3.2. Effects of scopolamine on task performance

A signal duration×retention interval×dose ANOVA demonstrated that the relative number of hits declined as the dose increased ($F(5,10)=6.679$, $p=0.006$; Fig. 1A). Also, the effects of the signal duration interacted with dose ($F(10,20)=2.823$, $p=0.023$). Subsequent analyses indicated that at the 500 ms signal duration, 0.3 mg/kg ($t(5)=4.606$, $p=0.006$) and 1.0 mg/kg scopolamine ($t(5)=2.827$, $p=0.037$) depressed the hit rate compared with saline. Correct rejections were analyzed using a retention interval×dose ANOVA. The relative number of correct rejections did not vary across drug dose. Omissions for each level of drug were analyzed utilizing a dose×trial type×retention interval ANOVA. Treatment with scopolamine significantly increased the omission rate ($F(5,25)=3.466$, $p=0.023$). Further t tests indicated that the omission rate was elevated following 1.0 mg/kg scopolamine compared with saline administration ($t(5)=2.808$, $p=0.038$). Fig. 1B shows the number of omissions per session following scopolamine administration. Notably, dose did not interact with trial type, retention interval, or, in a separate ANOVA, with signal duration for any analyses of omissions.

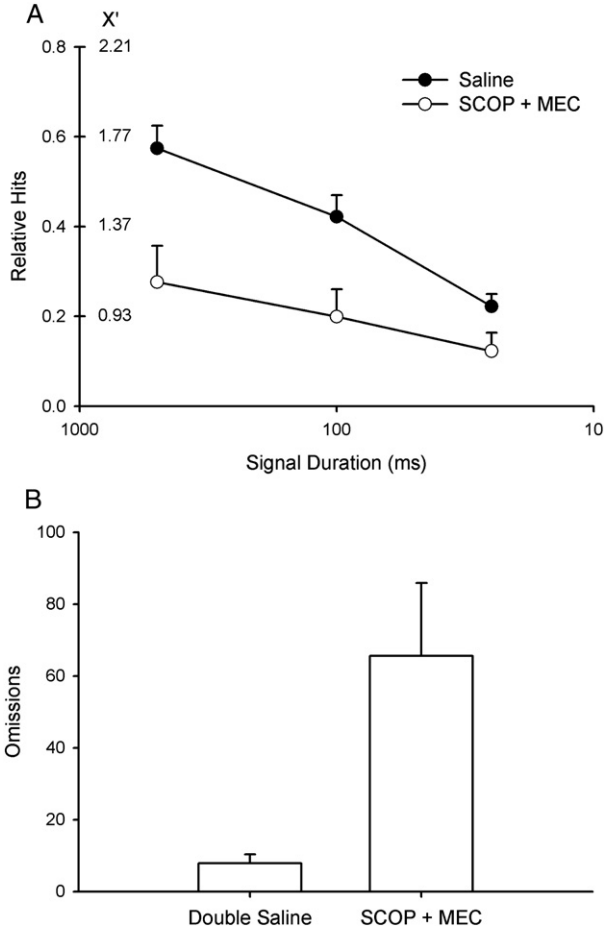

Fig. 3. The top figure (A) represents the relative number of hits (transformed values are presented inside of the axis for comparison) across signal duration following administration of 0.05 mg/kg scopolamine and 1.0 mg/kg mecamylamine (SCOP+MEC) or two injections of saline. Compared to saline, administration of scopolamine and mecamylamine decreased the hit rate. The bottom figure (B) represents the number of omissions per session (out of 162 total trials) following administration of saline or a combination of 0.05 mg/kg scopolamine and 1.0 mg/kg mecamylamine. The omission rate was elevated following scopolamine and mecamylamine compared to the saline administration. Error bars represent SEMs.

3.3. Effects of mecamylamine on task performance

A signal duration × retention interval × dose ANOVA for hits and a retention interval × dose ANOVA for correct rejections indicated that mecamylamine did not affect either of these measures of accuracy (Fig. 2A). Omissions following mecamylamine administration were analyzed utilizing a dose × trial type × retention interval ANOVA for signal trials and a dose × retention interval ANOVA for non-signal trials. Mecamylamine did increase omissions ($F(3,15)=7.147$, $p=0.012$). Post hoc t tests indicated that the omission rate was elevated following 5.0 mg/kg mecamylamine compared with saline administration ($t(5)=2.941$, $p=0.032$). There were no significant interactions in these analyses, nor did dose interact with signal duration. Mecamylamine-induced changes in omissions are shown in Fig. 2B.

3.4. Effects of combination drug treatment on task performance

One animal was excluded from all analyses because that animal did not perform any lever presses following combination drug administration. A signal duration × retention interval × dose ANOVA indicated that combination administration of scopolamine and mecamylamine decreased hits compared to saline ($F(1,10)=9.363$, $p=0.012$; Fig. 3A). A retention interval × dose ANOVA demonstrated that combination drug treatment had no effects on correct rejections. Omissions were analyzed using a dose × trial type × retention interval ANOVA. This analysis yielded a significant effect of dose ($F(1,10)=7.338$, $p=0.022$; Fig. 3B) and a significant dose × trial type × retention interval interaction ($F(2,20)=6.677$, $p=0.012$). Separate trial type × retention interval ANOVAs for saline and scopolamine/mecamylamine administration yielded a significant trial type × retention interval ANOVA following saline administration ($F(2,20)=7.831$, $p<0.003$) but not following scopolamine/mecamylamine administration. Further examination of the data suggested that the significant interaction was spurious and primarily due to the relatively low omission rates and low variability (<2 omissions at each retention interval for signal or non-signal trials) following saline administration.

A dose × signal duration ANOVA for omissions yielded a significant dose × signal duration interaction ($F(2,20)=12.96$, $p<0.001$). Post hoc t tests revealed that, following combination drug administration, the omission rate was significantly lower following the 25 ms signal compared with the 100 ms ($t(10)=3.39$, $p=0.007$) or the 500 ms signal ($t(10)=3.38$, $p=0.007$; Fig. 4).

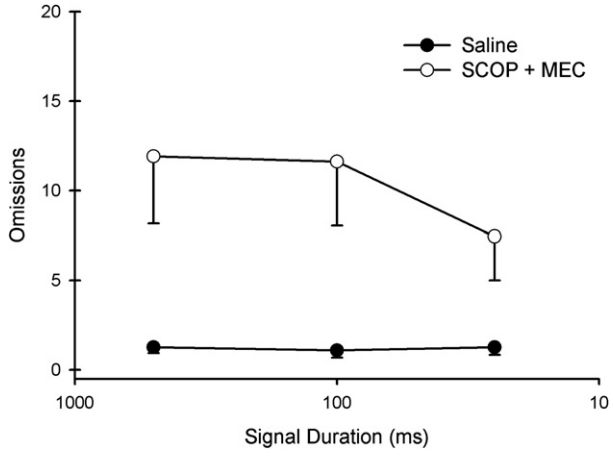

Fig. 4. The figure depicts omissions (ordinate) during signal trials, with the abscissa representing signal durations, following scopolamine and mecamylamine (SCOP + MEC) or saline administration (Saline). The omission rate did not vary across signal durations following saline administration. Following scopolamine and mecamylamine, the omission rate was lower during trials with a 25 ms signal duration compared with a 100 ms or 500 ms signal duration. Error bars represent SEMs.

4. Discussion

4.1. Effects of cholinergic receptor antagonists on task performance

The present experiment investigated the effects of cholinergic receptor blockade on a previously validated test of attention in the rat (McGaughy and Sarter, 1995) with a retention interval incorporated into the task. Scopolamine administration (0.3 and 1.0 mg/kg) decreased the accuracy of signal detection. These deficits did not extend to detection of non-signals, as the correct rejection rate remained stable across all drug administration conditions. The lack of drug-induced effects on correct rejections indicates that scopolamine did not interfere with the rat's ability to process the response rules of the task or did not lead to exclusive pressing of one lever (the correct rejection/miss lever). The lack of drug-induced effects on the correct rejection rate is also important for interpreting whether the decline in the hit rate following scopolamine administration reflects "chance" performance (near or below 50% averaged across retention intervals; Fig. 1A). If rats were responding at chance, both the hit rate and the correct rejection rate would be expected to be near 50%. Thus, the lack of effects of scopolamine on correct rejections suggests that scopolamine produced a decrease in signal detection that cannot be entirely attributed to an ability to respond based on the rules of the task, a bias to press one lever exclusively, or entirely random (chance) responding. Scopolamine-induced impairments in signal detection correspond with another experiment demonstrating that the integrity of basal forebrain corticopetal cholinergic neurons is necessary for signal detection in this task without a retention interval (McGaughy et al., 1996). Furthermore, intra-basalis infusions of benzodiazepine receptor agonists (Holley et al., 1995) or n-methyl-D-aspartate receptor antagonists (Turchi and Sarter, 2001), manipulations known to decrease cortical acetylcholine release (Fadel et al., 2001; Moore et al., 1995), also decrease the hit rate in the attention analog to the present task. However, specific interpretations of the depressed hit rate in terms of attention need to be tempered by the corresponding increase in the omission rate at the highest dose of scopolamine.

Mecamylamine increased omissions but did not affect accuracy in this task. Previous studies assessing the effects of mecamylamine on attention have demonstrated varied impairments in accuracy, latency, and omitted trials (Grottick and Higgins, 2000; Mirza and Stolerman, 2000; Turchi et al., 1995). It

has been suggested that many of the effects of mecamylamine on attentional task performance may be mediated by the actions of this drug as an *n*-methyl-D-aspartate (NMDA) receptor antagonist. In the attention analog to the present task (without a retention interval), administration of NMDA receptor antagonists ketamine (Nelson et al., 2002) and dizocilpine (Howe et al., unpublished observations) significantly elevate the omission rate. In the five-choice serial reaction time task, Grottick and Higgins (2000) reported deficits in response latency and accuracy following treatment with a 3.0 mg/kg dose of mecamylamine in rats, while Mirza and Stolerman (2000) reported increases in response latencies and omissions over a comparable dose range (1.6–5.0 mg/kg). Grottick and Higgins (2000) were not able to reproduce the effects of mecamylamine on the five-choice serial reaction time task with the nicotinic receptor antagonists methyllycaconitine or di-hydro-β-erythroidine, but did report that the NMDA receptor antagonist dizocilpine produced similar effects to mecamylamine. Thus, based on data from both the attentional analog to the present task and from the five-choice serial reaction time task, it appears that at least some of the effects of mecamylamine may be due to blockade of NMDA receptors. Increases in omissions are typically thought to reflect non-attentional or non-mnemonic aspects of task performance, such as disruption of motoric capabilities or of motivation for reward. It is most parsimonious to conclude that high doses of scopolamine and mecamylamine disrupted non-specific aspects of performance in the present task.

One goal of the present experiment was to assess whether cholinergic receptor antagonists differentially disrupt performance when a retention interval was introduced. Following saline administration, the hit rate was decreased following the longest (10 s) retention interval, supporting the contention that working memory was taxed in the present experiment. However, neither scopolamine nor mecamylamine (or combinations of subthreshold doses of these drugs) differentially disrupted performance as the retention interval was increased. Several other studies have found that scopolamine produces a retention interval dependent deficit, that is, a decrease in accuracy that is augmented when the retention interval is increased (Clissold et al., 1992; Pontecorvo et al., 1991; Shannon et al., 1990; but see Han et al., 2000; Herremans et al., 1995). The present experiment suggests that using a sufficiently attention-demanding procedure may be an important factor in revealing deficits at short retention intervals following scopolamine administration. These data suggest that the deficits associated with muscarinic and nicotinic receptor blockade in the present experiment are not exclusively due to deficits in working memory.

Previous experiments have examined the effects of scopolamine and mecamylamine on a version of this task that does not include a retention interval. These experiments demonstrated performance decrements at doses lower than those in which deficits were observed in the present experiment (Bushnell et al., 1997; Rezvani et al., 2002). The extensive training received by animals in the present experiment may contribute to the differences between the results in the present experiment and in previous experiments. Animals were trained for approximately one extra month to reach stable performance levels when the retention interval was introduced and were exposed to several task manipulations (see Burk, 2004) before the pharmacological treatments in the present experiment. These previous experiments also demonstrated that scopolamine and mecamylamine administration disrupted accuracy on non-signal trials. The lack of effects of scopolamine and mecamylamine on correct rejections in the present experiment may have been a result of the retention interval functionally serving to increase the inter-trial interval on non-signal trials. Decreasing the rate at which trials occur is known to enhance attentional performance (Parasuraman et al., 1987). Thus, the longer inter-trial interval on non-signal trials in the present experiment may have rendered non-signal trials "easier" than in previous experiments (in which a retention interval was not included in the task) by decreasing the rate of onset of non-signal trials.

4.2. Effects of co-administration of scopolamine and mecamylamine on task performance

Co-administration of scopolamine (0.05 mg/kg) and mecamylamine (1.0 mg/kg) decreased signal detection and increased omissions. Detection of non-signals remained unchanged. These drug doses did not affect task performance when administered alone. To our knowledge, combination administration of scopolamine and mecamylamine has not been assessed in the attention analog to the present task. However, the present findings do agree closely with previously observed results of combination scopolamine and mecamylamine treatment in the five-choice serial reaction time task (LeBlond et al., 2002; Mirza and Stolerman, 2000; but see Maviel and Durkin, 2003). The omission rate following scopolamine and mecamylamine was lowest following the 25 ms signal compared with the two longer signal durations. This significant effect of signal duration may reflect that the 25 ms signal was, more often than other signal durations, misidentified as a non-signal. As drug treatment failed to affect accurate detection of non-signals throughout the experiment, rats may have been more likely to perform a response on trials that the animal identified as a non-signal (even if the animal was incorrect in identifying the 25 ms signal as a non-signal). Thus, following combined scopolamine and mecamylamine administration, the rat may have been biased to respond more frequently on trials identified as non-signals. The decreased accuracy and increased omission rate when scopolamine and mecamylamine were co-administered (compared with when these drug doses were administered alone) suggests that the blockade of the additional cholinergic receptor subtype was critical for disrupting performance. That is, the additional blockade of both receptor subtypes was necessary to disrupt performance compared with the receptor blockade produced by these same doses when the scopolamine or mecamylamine was individually administered. Thus, the results from co-administration of scopolamine and mecamylamine support the idea that muscarinic and nicotinic receptors contribute to performance in the present task. Previous studies have suggested that some threshold of damage to the cholinergic system must be reached to impair performance, at least in spatial working memory tasks (Wrenn et al., 1999). The present data partially support this idea, as a low

dose of either drug was insufficient to affect performance but increasing the dose of scopolamine or blocking both nicotinic and muscarinic receptors disrupted task performance.

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