Pharmacology Biochemistry & Behavior, Vol. 31, pp. 337–343. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Effects of an Irreversible Muscarinic Agonist (BM123) on Avoidance and Spontaneous Alternation Performance

DAVID H. OVERSTREET,[1] RUTH A. BOOTH AND DONALD J. JENDEN

Department of Pharmacology, Center for the Health Sciences and Brain Research Institute, University of California, Los Angeles, CA 90024

Received 20 January 1987

OVERSTREET, D. H., R. A. BOOTH AND D. J. JENDEN. *Effects of an irreversible muscarinic agonist (BM123) on avoidance and spontaneous alternation performance*. PHARMACOL BIOCHEM BEHAV 31(2) 337–343, 1988.—The present study sought to assess whether the compound N-[4-(2-chloro-ethylmethylamine)-2-butynyl]-2-pyrrolidone (BM123), a potent muscarinic agonist that binds irreversibly to the muscarinic receptor (mAChR), has long-lasting functional effects which may be related to a reduction in functional mAChRs. Passive (inhibitory) avoidance performance, one-way active avoidance learning, and spontaneous alternation behavior were studied in rats. The results confirmed the acute muscarinic stimulating effects of BM123, including tremor, salivation, chromodacryorrhea and hypothermia. In addition, when measured 3–4 days after administration, rats treated with BM123 had disrupted spontaneous alternation performance and tended to have impaired performance for the inhibitory avoidance task with facilitated acquisition of active avoidance. This spectrum of effects is consistent with previous reports showing a 20–40% reduction in mAChRs at these times after BM123. The reversible muscarinic agonist, oxotremorine, was without significant effect. In a further experiment, it was found that pretreatment with methyl atropine did not prevent the disruption of spontaneous alternation behavior by BM123, whereas pretreatment with atropine did. Thus, these long-lasting behavioral effects of BM123 are related to its alkylation of and subsequent reduction in central mAChRs.

Irreversible muscarinic agonist BM123 Muscarinic receptors (mAChR) Passive avoidance
One-way active avoidance Spontaneous alternation

THE introduction of a B-chloroethylamino group into the structure of oxotremorine, a potent, reversible muscarinic agonist, has resulted in a number of compounds that have proved useful in investigating cholinergic mechanisms (14,15). These compounds, N-[4-(2-chloroethylmethylamino)-2-butynyl]-2-pyrrolidone (BM123) and N-[4-(2-chloromethylpyrrolidino)-2-butynyl]-2-pyrrolidine (BM130), cyclize spontaneously in neutral aqueous solutions to form aziridinium ions which are responsible for their irreversible binding to the muscarinic acetylcholine receptor (mAChR) (3, 4, 16). Various studies indicate that the initial, acute effects of these compounds are similar to that of oxotremorine (e.g., tremor, hypomotility) (19,20). In a direct comparison of BM123 and oxotremorine, it was reported that BM123 had generally longer lasting effects than did oxotremorine on a number of behavioral and physiological variables, a finding consistent with its putative action as an irreversible agonist (20).

Much less is known about the long-term consequences of BM123 administration (7,19). Because of an earlier report that learned responses recovered in a similar time frame to the recovery of mAChR following BM123 administration (20), behavioral tasks sensitive to blockade of mAChR were selected to examine further the long-lasting functional effects of BM123. The passive (inhibitory) avoidance and spontaneous alternation paradigms were selected because of the extensive evidence indicating that drugs which block mAChR disrupt performance of these two tasks (6, 8, 9, 13, 22), while the one-way conditioned avoidance (active) paradigm was selected because of the evidence that these drugs facilitate acquisition of this task (1,17). It was predicted that BM123 would disrupt inhibitory avoidance and spontaneous alternation, but would facilitate acquisition of one-way active avoidance.

METHOD

Animals

The animals were male Sprague-Dawley rats (Simonsen Labs, Gilroy, CA). They weighed 260–280 g at the commencement of the experiments and were housed individually

[1]Present address: School of Biological Sciences, The Flinders University of South Australia, Bedford Park, S.A. 5042, Australia.

in a temperature- (22±1°C) and humidity- (50%) controlled room on a 12:12 light-dark cycle (lights on at 07:00).

Apparatus

Core body temperatures were recorded by inserting either a YSI thermistor probe or a Bailey thermocouple 6 cm into the rectum of the rat and recording the output on a YSI digital telethermometer or a Bailey Model BAT-12 recorder. Preliminary studies established that these two instruments gave virtually identical body temperature readings (0.1°C).

Locomotor activity was recorded in circular open field chambers, fitted with banks of photocells. One set was located 4 cm above the floor and gave a record of horizontal activity; a second set was located 12 cm above the floor and gave a record of vertical activity. The output of these photocells was fed via an interface system to a TRS-80 microcomputer which cumulated the counts at one-minute intervals and printed them out at the end of the 10-min session.

Passive avoidance was measured in a step through apparatus similar to that used extensively by McGaugh and colleagues (10). This apparatus consisted of a small compartment made of white plastic and a large compartment made of stainless steel sheets. These sheets were in series with a shock generator which ensured a current flow of preset mA when activated.

One-way active avoidance was measured in the apparatus described by Russell and Macri (18). It consisted of a U-shaped alley constructed of stainless steel in series with a shock generator, which ensured delivery of a preset current flow when activated. Placing an animal in the alley completed the circuit. A timer programmed the onset of the conditioned stimulus (tone), and the unconditioned stimulus (shock).

Spontaneous alternation was measure in a T-maze with walls constructed out of wood and painted brown. The arms of the maze were 13 cm wide and 30 cm deep. The 40 cm start arm was separated from the 30 cm chocie arms by a guillotine door. The T-maze did not have a floor but was placed on a stainless steel surface to facilitate cleaning between trials.

Experiment 1

After two days of individual handling, the rats were placed in the open field chambers for a baseline recording of locomotor activity. On the next day 10 rats received three consecutive injections of BM123 (8, 20, 50 μmol·kg^{-1}, IV) at hourly intervals according to the regimen initiated by Russell *et al.* (20), while another 10 rats received corresponding volumes of the vehicle. Temperatures were recorded 15, 30 and 60 min after each injection and the following general signs of cholinergic stimulation observed: tremors, salivation and chromodacryorrhea.

Three days after this series of injections the rats were placed again in the open field chambers to obtain a 10-min recording of locomotor activity. This time was selected because locomotor activity has recovered by this time but mAChR concentrations are still reduced (20). Shortly thereafter they were placed in the white compartment of the passive avoidance apparatus. Upon entering the dark, stainless steel compartment, a partition was raised to prevent escape and a 0.25 mA footshock was delivered for 0.2 sec. The rats were then removed from the apparatus. Retention was tested 24 hr later by placing the rat in the white compartment and recording the time, to a limit of 5 min, to enter the dark section.

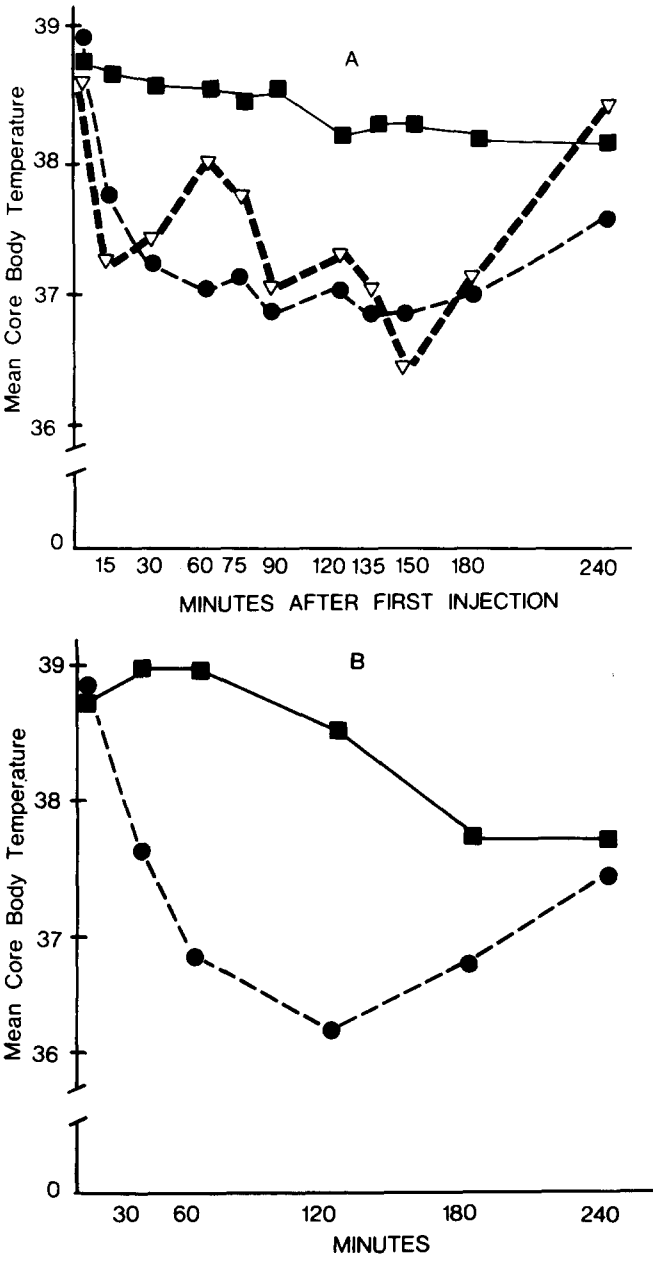

FIG. 1. The effects of BM123 and oxotremorine on core body temperature in rats: (A) represents the mean temperature for eight rats after a series of three IV injections of BM123 (8, 20, 50 μmol·kg^{-1}) given at 0, 60 and 120 min (●) or after a series of three IV injections of oxotremorine (0.3, 0.75, 1.88 μmol·kg^{-1}) given at 0, 60 and 120 min (▽), or after sham injections (■). (B) represents the mean temperatures for 12 rats after a single IV injection of BM123 (63 μmol·kg^{-1}) given at time 0 (●) or after sham injections (■). All values for BM123 are significantly less than the sham-treated values except for 240 min.

Immediately after retention in the passive avoidance apparatus was tested, the rats were placed in the runway for study of one-way active avoidance learning. After a 20 sec

TABLE 1

EFFECTS OF TREATMENT WITH BM123* OR OXOTREMORINE ON PASSIVE AVOIDANCE

Pretreatment	N	Median Latency to Enter on Training (Seconds)	Median Latency to Enter on Retention (Seconds)
Experiment 1			
BM123	10	12	197†
Vehicle	10	16	300
Experiment 2			
BM123	8	14	447
Sham	7	7	400
Oxotremorine	8	17	600

*In Experiment 1 the rats were allowed 300 sec to make a response. In Experiment 2 they were allowed 600 sec.

†Significantly different, $p<0.05$, from saline control group, Mann-Whitney U-test.

delay, the guillotine door was raised simultaneously with the sounding of a 68 decibel tone. If the rat did not move to the other end of the runway within 10 sec, it received a 0.5 mA footshock until it escaped. A performance of seven correct avoidance responses in 10 trials was used as the criterion for learning. Rats which did not meet this criterion within 50 trials were given a score of 50+.

Experiment 2

Two modifications were introduced in this experiment. The effects of oxotremorine, a reversible agonist, were studied and spontaneous alternation was included as a third behavioral measure. After two days of individual handling, baseline alternation testing was conducted, following the procedure of Scheff and Cotman (21) with minor modifications. Animals tended to habituate if only 50 min elapsed between trials, so a procedure was adopted in which two trials per day were held, the first between 07:00 and 09:00 and the second between 16:00 and 18:00. Each trial consisted of a forced run followed by a choice run. On the forced run the rat was placed in the start box and one arm was blocked. After 10 sec, the door was raised and the rat allowed 60–120 sec to enter the open arm. It was confined there for 20 sec, then returned to the start arm for 10 sec. The choice run began by lifting the guillotine door. If an animal entered the previously blocked arm, the response was scored as an alternation. Half the animals in each group were given forced runs to the right, the other half given forced runs to the left. Any individual rat was maintained in the same condition (forced-right or forced-left) throughout the experiment.

After the completion of 6 trials, 8 rats received three consecutive IV injections of BM123 (8, 20, 50 μmol·kg^{-1}), as described above; 8 rats received three consecutive IV injections of oxotremorine (0.3, 0.75, 1.88 μmol·kg^{-1}) and 8 rats received sham treatment (needle insert but no injection).

Frequencies of spontaneous alternation were recorded 24, 48 and 72 hr after this series of injections and locomotor activity was measured 72 hr after the injections. Passive avoidance training and retention were carried out 72 and 96 hr after the injections and active avoidance testing was conducted at 96 hr after the injections. The conditions for the latter tests were similar to those for Experiment 1, with the exceptions that the shock level for the active avoidance test was reduced to 0.35 mA and the animals were given 10 min to make a response on the retention test in the passive avoidance apparatus. The shock level for active avoidance was reduced because some rats in Experiment 1 appeared over reactive. The time in the passive avoidance test was extended to 10 min in an attempt to avoid truncated scores (with many rats at the maximum score).

Experiment 3

Recent evidence from research by our colleagues (Crocker *et al.*, in preparation) indicates that a single high dose of BM123 is as effective in reducing muscarinic receptors as the series of three doses used in Experiments 1 and 2 without producing mortality. After individual handling and pretraining on spontaneous alternation, 12 rats received a single IV injection 63 μmol·kg^{-1} BM123, while another 12 received sham injections. Temperatures were recorded at hourly intervals. Locomotor activity was recorded 24 hr after the injections to determine consequences of this single dose regimen on this variable. Spontaneous alternation was assessed at 24, 48 and 72 hr after the injection. Avoidance performance was not recorded in this experiment because of the inconsistent results observed in Experiments 1 and 2.

Experiment 4

This experiment was designed to determine whether the disruptive effects of BM123 on spontaneous alternation behavior were the consequences of peripheral and/or central alkylation of muscarinic receptors. After individual handling and pretraining on spontaneous alternation, 8 rats received either saline (1 ml·kg^{-1}, SC), methyl atropine (5 μmol·kg^{-1}, SC) or atropine (5 μmol·kg^{-1}, SC) 40 min prior to the IV injection of BM123 (63 μmol·kg^{-1}). Another 6 rats were pretreated with saline (2), methyl atropine (2) or atropine (2), but were not given an injection of BM123. Core body temperatures were recorded at hourly intervals for 4 hr and locomotor activity was recorded for 20 min at 8 hr after these injections. Alternation testing continued daily for three days after the injections.

Statistical Analysis

Nonparametric statistics, Kruskal-Wallis tests and

TABLE 2

EFFECTS OF TREATMENT WITH BM123 OR OXOTREMORINE ON ONE-WAY ACTIVE AVOIDANCE*

Pretreatment	N	Median Trials to Criterion
Experiment 1		
BM123	10	11
Vehicle	10	13
Experiment 2		
BM123	8	2†
Sham	8	10
Oxotremorine	8	4

*The shock level was 0.5 mA in Experiment 1 and 0.35 mA in Experiment 2.

†Significantly different, $p<0.05$, from sham group, Mann-Whitney U-test.

Mann-Whitney U-tests were used to examine differences between independent groups and Wilcoxon tests to analyze differences within group.

RESULTS

Acute Effects of BM123

The three-dose regimen of both BM123 and oxotremorine produced hypothermic effects which were dose-dependent, as illustrated in Fig. 1A. The hypothermic effects of BM123 were longer lasting than those of oxotremorine. As can be seen in Fig. 1B, the hypothermic effects of a single dose of 63 μmol·kg^{-1} BM123 were also long lasting and comparable to those seen after the triple dose regimen (Fig. 1A).

The cholinomimetic signs observed after BM123 or oxotremorine were similar, but not identical. Both compounds produced salivation, chromodacryorrhea, and tremor in virtually all animals within one min after the IV injection. Tremor disappeared within 15 min for both compounds, chromodacryorrhea within 30 min for oxotremorine and 60 min for BM123 and salivation within 60 min for oxotremorine but not for BM123. Thus, the effects of BM123 lasted longer than those of oxotremorine.

Passive Avoidance

The effects of treatment with BM123 or oxotremorine on passive avoidance training and retention are summarized in Table 1. There were no significant effects on latency to enter on the training trial, suggesting that BM123 no longer had any effects on locomotor activity at three days after injection. The results of the test of locomotor activity carried out before the training trial in the passive avoidance apparatus confirmed the lack of effects (data not shown).

In the first experiment the majority of the control animals (80%) stayed in the small plastic compartment for the full duration of the retention test, while relatively few (30%) of the BM123-treated rats did so; consequently, a significant impairment of retention was seen in the BM123-treated rats. However, a similar impairment was not evident in Experiment 2, where the duration of the retention trial was increased in an attempt to detect an even bigger difference.

Active Avoidance

Effects of treatment with BM123 or oxotremorine on acquisition of one-way active avoidance are summarized in Table 2. There was only a very slight trend for the BM123-treated to learn more rapidly in the first experiment. However, when the shock level was reduced in the second experiment, the BM123-treated rats learned the task significantly more rapidly than the sham control group. In fact, all of the BM123-treated rats learned the task in 5 trials or less. The performance of the oxotremorine-treated group was intermediate between the other two, but not significantly different from the sham-treated group.

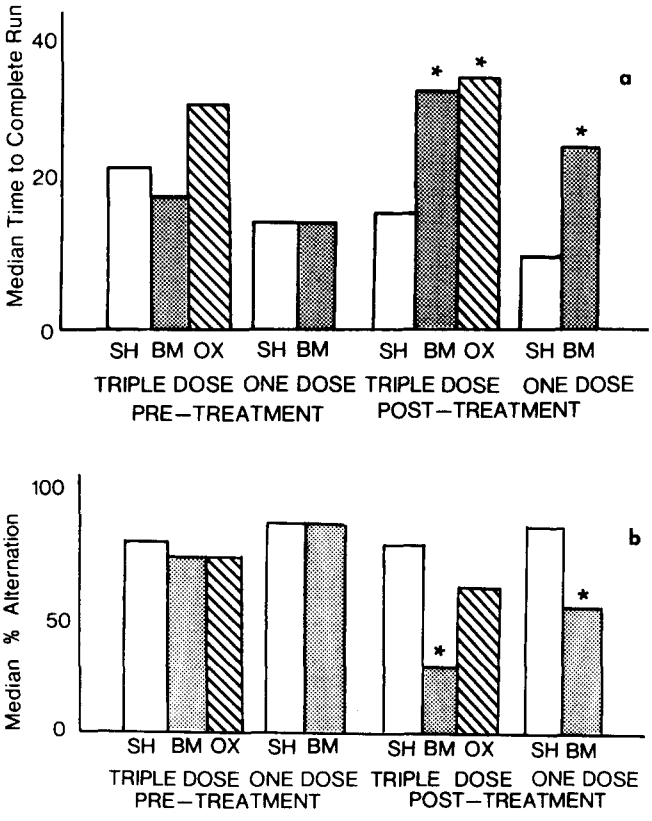

FIG. 2. The effects of BM123 and oxotremorine on time to run and spontaneous alternation in a T-maze. (a) Median time to complete a run in the T-maze for eight rats in each group for the triple dose regimen and 12 rats in each group for the single dose regimen. (b) Median % spontaneous alternation for eight rats in each group for the triple dose regimen and 12 rats in each group for the single dose regimen. *Significantly different from sham-treated group, $p<0.05$, Mann-Whitney U-tests.

Spontaneous Alternation

The rates of spontaneous alternation and times to complete a trial in Experiments 2 and 3 are illustrated in Fig. 2. There are three general features of note in this figure: 1) There were no significant differences among the frequencies of alternation and running times during the baseline period; 2) sham-treated and oxotremorine-treated rats exhibited no significant change in alternation frequencies, whereas those for BM123-treated rats were significantly reduced; 3) both the oxotremorine- and BM123-treated rats exhibited a significant increase in running times. Statistical analysis of these data was conducted by Mann-Whitney U-tests of the differences between baseline and treatment conditions (6 trials

TABLE 3

EFFECTS OF ATROPINE (5 μmol·kg⁻¹) AND METHYL ATROPINE (5 μmol·kg⁻¹) PRETREATMENT ON THE HYPOTHERMIC EFFECTS OF BM123 (63 μmol·kg⁻¹)

Treatment Group	Mean Deviation From Baseline Temperature ± SE			
	1 hr	2 hr	3 hr	4 hr
Sham	+0.3 ± 0.2	−0.3 ± 0.2	−0.5 ± 0.2	−0.4 ± 0.3
BM123	−2.0 ± 0.1*	−2.7 ± 0.1*	−2.1 ± 0.1*	−1.5 ± 0.1
Methyl atropine + BM123	−2.0 ± 0.1*	−1.8 ± 0.2†	−1.4 ± 0.2†	−1.1 ± 0.2
Atropine + BM123	−2.0 ± 0.2*	−1.2 ± 0.2†	−0.5 ± 0.2†	−0.4 ± 0.1†

*Significantly different from sham-treated group ($p<0.05$).
†Significantly different from group treated with BM123 only ($p<0.05$).

over 3 days). Such analyses indicated that the alternation performance of the BM123-treated rats was significantly reduced in both experiments. In addition, the running times for both oxotremorine and BM123 were significantly elevated.

Thus, BM123 both reduced activity and frequency of alternation. However, data from individual days indicated that, whereas alternation performance tended to be stable over days, the running times were slowest on Day 1 and fastest on Day 3. Locomotor activity data confirmed these impressions. On Day 1 the locomotor activity of the BM123-treated rats was 18.8% of baseline for vertical and 25.4% of baseline for horizontal activity, compared to 109.0% and 105.0% for the sham controls ($U=0$, $p<0.001$ in both cases). The corresponding values on Day 3 were 83.6% vertical and 77.3% horizontal for BM123-treated and 77.4% vertical and 80.0% horizontal for sham controls ($p>0.05$%).

The effects of pretreatment with methyl atropine and atropine on the hypothalamic effects of BM123 are summarized in Table 3. It can be seen that there was a partial protection of the hypothermic effects, with atropine having a greater effect. Observation of general signs also supported this conclusion; both atropine- and methyl atropine-pretreated groups exhibited less salivation than saline-pretreated rats and none exhibited chromodacryorrhea. Slight tremors were seen in some atropine-pretreated rats and more marked tremors were seen in methyl atropine-pretreated rats. All groups exhibited large reductions (75%) in locomotor activity at 8 hours after the BM123 injections. However, the atropine-pretreated rats were slightly but significantly more active than the saline- or methyl atropine-pretreated rats (data not shown).

The effects of pretreatment with methyl atropine and atropine on BM123's effects on spontaneous alternation behavior are illustrated in Fig. 3. Analyses of these data were conducted with nonparametric statistics, based on the difference scores (pre-posttreatment). All BM123-injected groups had significantly greater running times in the T-maze, although the atropine-pretreated group was less impaired than the other two groups (Fig. 3a). In contrast to the running times, only the methyl atropine- and saline-pretreated groups exhibited deficits in alternation behavior (Fig. 3b). Thus, although the atropine-pretreated group exhibited an increase in running times, they still alternated at high frequencies characteristic of the control group.

DISCUSSION

Previous workers have established that memory of passive avoidance varies inversely with changes in the concentration of mAChR brought about by chronic drug regimens (5,12). Consequently, we chose to examine passive avoidance performance in BM123-treated rats at a time when the locomotor-depressant effects are largely dissipated but brain mAChR concentrations are still only 60–80% of normal (20). The data from only one of the two experiments reported in this study found evidence of an impairment of performance in BM123-treated rats (Table 2), providing only partial support for the hypothesis. Thus, giving the rats 10 min to move into the previously shocked chamber instead of 5 min did not lead to a more significant result.

The data on active avoidance learning also partially support the contention that reduction in mAChR induced by BM123 has functional consequences 3–5 days after acute administration. The BM123-treated rats exhibited a significantly facilitated acquisition of the task at the lower shock level. Other workers have reported significantly facilitated acquisition of active avoidance following administration of drugs which block mAChR (1,17). Such observations are consistent with the hypothesis that the facilitation of active avoidance in BM123-treated rats is related to the reduced concentration of mAChR (20). The failure to see this facilitated acquisition in the first experiment may be related to the higher shock level to which some BM123-treated rats may have overreacted.

There are difficulties in using passive and active avoidance paradigms to study the time course of BM123's effects due to the limitation of only one testing of an animal. Consequently, large groups of rats would be needed to explore the time-dependent aspects of BM123 on learning/memory measures. For this reason and because there were inconsistent effects in the two experiments, spontaneous alternation was selected as an additional task which had the advantage that daily testing of the rats was possible. This task is sensitive to the administration of both stimulation and blockade of mAChR, depending on the conditions of testing (22). Because of the results on passive avoidance in Experiment 1, we chose conditions which would result in high levels of alternation in normal rats in order to detect an effect related to reduced mAChRs. Such an effect was dramatically

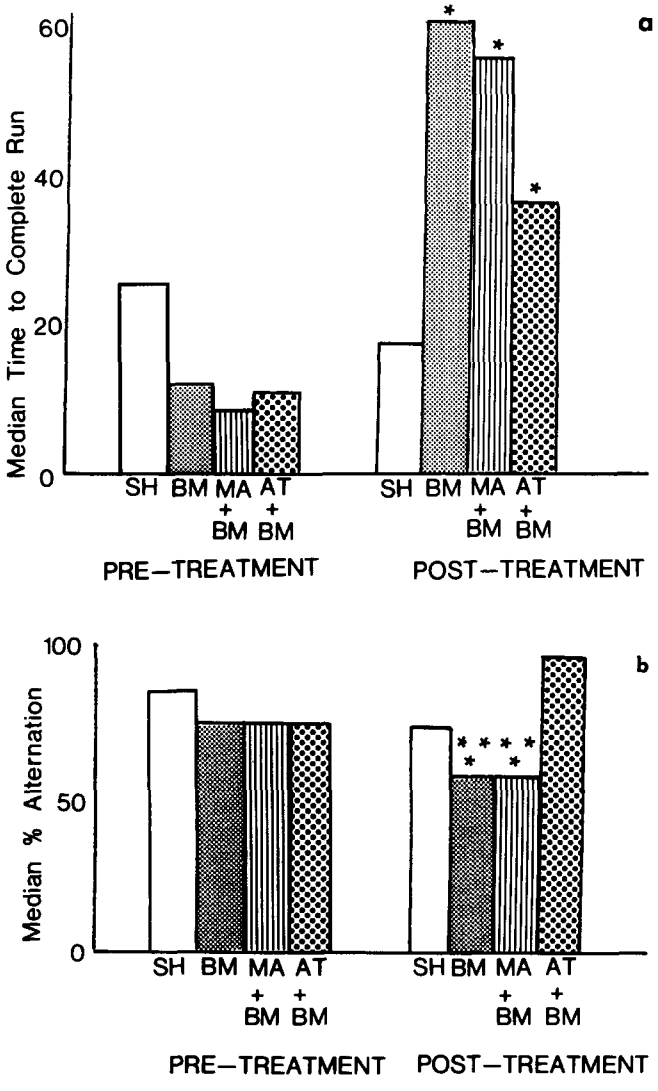

FIG. 3. The effects of atropine and methyl atropine pretreatment on BM123-induced alterations in time to run and spontaneous alternation in a T-maze. (a) Median time to complete a run in the T-maze for 6 rats in the SH group and 8 rats in the other three groups. (b) Median % spontaneous alternation for 6 rats in the SH group and 8 rats in the other three groups. SH=sham treatment; BM=BM123 (63 μmol·kg^{-1}); MA + BM = methyl atropine (5 μmol·kg^{-1}) 40 min before BM123; AT + BM = atropine (5 μmol·kg^{-1}) 40 min before BM123. *Significantly different, $p<0.05$, from sham-treated group. **Significantly different, $p<0.05$, from AT + BM group.

apparent in Experiment 2 when the BM123-treated rats actually alternated at rates substantially less than 50%. Therefore, the results on spontaneous alternation performance clearly indicate that BM123 is producing an effect which has been associated with a blockade of mAChR. Moreover, the daily trial results indicate that this effect may appear as early as 24 hr when the rats are still hypomotor.

Although the literature is quite consistent in the reports of disruption of spontaneous alternation performance by mAChR blockade, there is some controversy over the interpretation of these effects. According to Heise (8), who has recently reviewed this literature, the earlier interpretation that this task is a reflection of habituation and the results indicative of mAChR blockade on habituation is not supported by a number of recent studies. Some authors had viewed spontaneous alternation as an index of short-term working memory and the disruption of alternation performance by mAChR blockade as evidence of memory-disruption effects (2, 11, 22, 23). This latter interpretation of the task suggests that the effect of BM123 treatment is evidence of an impairment of short-term memory resulting from a decrease in density of mAChRs.

The results of the final experiment (Fig. 3) suggest that the disruptive effects of BM123 on spontaneous alternation behavior are a consequence of its alkylation of central mAChR, because atropine, a centrally acting anti-muscarinic agent, prevented its effects whereas methyl atropine, which does not have central actions, did not. Other workers have shown that prior treatment with competitive antagonists such as atropine prevent the alkylation of mAChR by BM123 (3, 4, 16). Consequently, differential behavioral results probably arise because of the prevention of alkylation of central mAChR by atropine but not by methyl atropine. However, neither agent completely abolished the acute effects of BM123 (Table 3) and atropine only marginally increased locomotor activity.

In summary, there is isolated evidence from the passive and active avoidance paradigms and consistent evidence from the spontaneous alternation paradigm to indicate that the behavioral effects seen in rats 3–4 days after treatment with the alkylating oxotremorine analog, BM123, are related to the reduction in the concentration of brain mAChR induced by this compound (20).

ACKNOWLEDGEMENTS

We thank James Randklev for constructing the T-maze, Sharlene Lauretz and Kennita Carter for their excellent technical assistance, Joy Noakes for her expert editorial assistance and Roger Russell for helpful suggestions. This work was supported by U.S. Public Health Service Grant MA 17691 and U.S. Army Research and Development Command Contract DAMD 17-83-C-3073.

REFERENCES

1. Barrett, R. J.; Leith, N. J.; Ray, O. S. Analysis of facilitation of avoidance acquisition produced by d-amphetamine and scopolamine. Behav. Biol. 11:189–203; 1974.
2. Brito, G. N. O.; Thomas, G. J. T-maze alternation, response patterning and septo-hippocampal circuitry in rats. Behav. Brain Res. 3:319–340; 1981.
3. Ehlert, F. J.; Jenden, D. J.; Ringdahl, B. An alkylating derivative of oxotremorine interacts irreversibly with the muscarinic receptor. Life Sci. 34:985–991; 1984.
4. Ehlert, F. J.; Jenden, D. J. Alkylating derivatives of oxotremorine have irreversible actions on muscarinic receptors. In: Hanin, I., ed. Dynamics of cholinergic function. New York: Plenum Press; 1985.
5. Gardner, R.; Ray, R.; Frankenheim, J.; Wallace, K.; Loss, M.; Robichaud, R. A possible mechanism for diisopropyl fluorophosphate-induced memory loss in rats. Pharmacol. Biochem. Behav. 21:43–46; 1984.

6. Giordano, M.; Prado-Alcala, R. A. Cholinergic blockade of the caudate nucleus and passive avoidance. Protection against retention deficits by increasing the value of the negative reinforcer. Soc. Neurosci. Abstr. 10:257; 1984.
7. Gyorgy, L.; Gellen, B.; Doda, M.; Sterk, L. Pharmacology of 1-(2-oxo-pyrrolidino)-4- (2-chloroethyl-methylamino) But-2-yne HCl (DSO 16), I: Its central cholinomimetic and cholinolytic effects in mice. Acta Physiol. Acad. Sci. Hung. 40:373–379; 1971.
8. Heise, G. A. Behavioural methods for measuring effects of drugs on learning and memory in animals. Med. Res. Rev. 4: 535–558; 1984.
9. Hingtgen, J. N.; Aprison, M. A. Behavioural and environmental aspects of the cholinergic system. In: Goldberg, A. M.; Hanin, I., eds. Biology of cholinergic function. New York: Raven Press; 1976:515–581.
10. Liang, K. C.; McGaugh, J. L. Lesions of the stria terminalis attenuate the enhancing effect of post-training epinephrine on retention of an inhibitory avoidance response. Behav. Brain Res. 9:49–58; 1983.
11. Livesey, P. J.; Livesey, D. J.; Syme, G. J. Spontaneous alternation in the white rat: A learning-memory phenomenon. Behav. Neural Biol. 32:158–169; 1981.
12. Loullis, C. C.; Dean, R. L.; Lippa, A. S.; Meyerson, L. R.; Beer, B.; Bartus, R. J. Chronic administration of cholinergic agents: Effects on behaviour and calmodulin. Pharmacol. Biochem. Behav. 18:601–604; 1983.
13. Overstreet, D. H. Behavioural plasticity and the cholinergic system. Prog. Neuropsychopharmacol. Biol. Psychiatry 8:133–151; 1984.
14. Overstreet, D. H.; Russell, R. W.; Booth, R. A.; Jenden, D. J. Influence of atropine and N-methyl atropine pretreatments on behavioral and physiological effects of the irreversible muscarinic agonist, BM123. Pharmacol. Biochem. Behav. 26:475–481; 1987.
15. Ringdahl, B.; Jenden, D. J. Affinity, efficacy and stereoselectivity of oxotremorine analogues for muscarinic receptors in the isolated guinea pig ileum. Mol. Pharmacol. 23:17–25; 1983.
16. Ringdahl, B.; Resul, B.; Ehlert, F. J.; Jenden, D. J.; Dahlbom, R. The conversion of 2-chloroalkylamine analogues of oxotremorine to azirindium ions and their interactions with muscarinic receptors in the guinea pig ileum. Mol. Pharmacol. 26:170–179; 1984.
17. Rosic, N.; Bokonjic, D.; Overstreet, D. H. Task-dependent development of tolerance to scopolamine. Pharmacol. Biochem. Behav. 13:183–186; 1980.
18. Russell, R. W.; Macri, J. Some behavioural effects of suppressing choline transport by cerebroventricular injection of hemicholinium-3. Pharmacol. Biochem. Behav. 8:399–403; 1978.
19. Russell, R. W.; Crocker, A. D.; Booth, R. A.; Jenden, D. J. Behavioural and physiological effects of an aziridinium analog of oxotremorine (BM130). Psychopharmacology (Berlin) 88:24–32; 1986.
20. Russell, R. W.; Smith, C. A.; Booth, R. A.; Jenden, D. J.; Waite, J. J. Behavioral and physiological effects associated with changes in muscarinic receptors following administration of an irreversible cholinergic agonist (BM123). Psychopharmacology (Berlin) 90:308–315; 1986.
21. Scheff, S. W.; Cotman, C. W. Recovery of spontaneous alternation following lesions of the entorhinal cortex in adult rats: Possible correlation to axon sprouting. Behav. Biol. 21:286–293; 1977.
22. Squire, L. R. Effects of pre-trial and post-trial administration of cholinergic and anticholinergic drugs on spontaneous alternation. J. Comp. Physiol. Psychol. 69:69–75; 1969.
23. Tobe, A.; Egawa, M.; Nagai, R. Effect of 4-(O-benzylphenoyl)-N-methyl-butylamine hydrochloride (MCI-2016) on the scopolamine-induced deficit of spontaneous alternation behaviour in rats. Jpn. J. Pharmacol. 33:775–784; 1983.