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Facilitation of Memory Performance by a Novel Muscarinic Agonist in Young and Old Rats

ANGELA C. RUSKE AND K. GEOFFREY WHITE

University of Otago, Department of Psychology, Dunedin, New Zealand

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RUSKE, A. C. AND K. G. WHITE. *Facilitation of memory performance by a novel muscarinic agonist in young and old rats.* PHARMACOL BIOCHEM BEHAV **63**(4) 663–667, 1999.—AF150(S), a partial M1 muscarinic receptor agonist, was tested for its ability to improve performance in rats in a delayed matching-to-position task. Young and old rats received intraperitoneal injections of 0, 1, and 4 mg/kg of AF150(S). AF150(S) significantly enhanced matching accuracy for both young and old rats. Fits of exponential functions to discriminability measures showed that the enhancement was manifest as a reduction in the rate of forgetting. These results indicate that AF150(S) may be a useful therapeutic agent for improving cognitive function. © 1999 Elsevier Science Inc.

Rats Memory Rate of forgetting Initial discriminability Delayed matching-to-sample
Cholinergic system Age AF150(S) Muscarinic agonist

THE role of the cholinergic system in cognitive function has attracted a great deal of interest over the years. In particular, the behavioral deficits believed to be associated with age-related neurophysiological changes to the cholinergic system have generated a lot of research. Bartus, Dean, Beer, and Lippa (3) first formally proposed the link between cholinergic function and age-related memory loss. This claim has been supported by numerous studies, which show that disruption to the cholinergic system (either by pharmacological manipulation or by lesions), produce behavioral deficits that emulate those seen in aged subjects. For example, Drachman and Leavitt (10) administered scopolamine, a centrally acting cholinergic antagonist, to young healthy human subjects and compared their performance on a battery of memory tests to that of aged subjects. The deficits caused by scopolamine administration closely resembled those found in aged subjects. Drachman (9) found similar behavioral deficits in young humans following scopolamine administration. A recent review by Everitt and Robbins (13) summarizes evidence that supports the role of the cholinergic system in cognitive function, and suggests that different cholinergic projections are involved in different cognitive processes.

Impaired memory performance following cholinergic disruption has been found in a variety of species, including monkeys (1,4,22,27), rats (11), and pigeons (32,34). Similarly, aged animals are impaired in memory tasks relative to their younger counterparts. For example Bartus (2) reported that aged monkeys showed poorer memory performance in a delayed matching-to-sample procedure relative to younger monkeys. Physostigmine reversed these aged-related memory deficits in some, but not all, of the aged monkeys. Gagnon and Winocur (18) found that aged rats took longer to acquire the delayed matching-to-sample task and also showed poorer memory performance than younger rats. Blokland, Honig, and Raaijmakers (5) reported that aged Lewis rats took longer than younger rats to find the hidden platform in a water maze procedure. They attributed this deficit to the impaired ability of the aged rats to use spatial cues.

Agents that enhance or mimic the action of acetylcholine (ACh) have been targeted for the treatment of age-related memory disorders. More recently attention has focused on developing agents that act selectively on M1 muscarinic cholinergic receptors, as these receptors are believed to be involved in learning and memory (25,28,38). The advantage of drugs that act selectively on the M1 muscarinic receptor is that severe peripheral side effects, attributed almost entirely to the activation of M2 and M3 receptors (12), can be avoided. A new M1 agonist, AF150(S), is an agent that shows promise for the treatment of disorders associated with cholinergic system dysfunction. This functionally selective partial M1 agonist, AF150(S)-[1-Methyl-piperidine-4-spiro-(2′-methylthiazoline)] is highly selective towards the M1 receptor, has a wide therapeutic window, and readily crosses the blood–brain barrier (7). It has been shown to be a highly selective full agonist in elevating calcium in CHO (Chinese hamster ovary) cells stably transfected with cloned m1 muscarinic receptors, and a partial agonist in stimulating phosphoinositides hydrolysis in CHO cells (17).

Brandeis et al. (7) investigated the pharmacodynamic pro-

Requests for reprints should be addressed to Geoff White, Department of Psychology, University of Otago, Dunedin, New Zealand.

file of AF150(S), and its ability to reverse AF64A-induced cognitive deficits in rats. They found the lethal dose of AF150(S) to be greater than 500 mg/kg, and the sign-free dose to be greater than 40 mg/kg, indicating a wide therapeutic window. Following bilateral intraventricular administration of AF64A, a neurotoxin that at low doses has been shown to destroy cholinergic neurons (16), rats were tested on a variety of behavioral tasks with doses of 0 (Double Distilled Water), 0.5, 1, and 5 mg/kg of AF150(S). They reported a significant attenuation of AF64A-induced impairments in all tasks. The most consistent dose at attenuating impairments across tasks was the 1 mg/kg dose level. Similarly, Ruske et al. (29) found that AF150(S) attenuated scopolamine-induced deficits in a delayed matching-to-sample procedure in pigeons.

The present study was concerned with the effects of AF150(S) on the matching accuracy of young and aged rats in a delayed matching-to-position (DMTP) procedure. Prior studies suggest that aged rats show memory impairments in DMTP compared to young (18), although a recent review by Gallagher and Rapp (20) indicates that there may be considerable individual differences in age-related cognitive impairment. Given that M1-receptor agonists are capable of enhancing memory (2,6), the present study, therefore, asked whether there would be age-related differences in matching performance following administration of AF150(S).

METHOD

Subjects

Ten young female Sprague–Dawley rats, 3 months of age at the beginning of the experiment and weighing between 220 and 240 g, and 10 old female Sprague–Dawley rats aged 19 months at the beginning of the experiment and weighing between 340 and 510 g, were used. The old rats had a previous history of DMTP training 6 months before the start of the present study. In this, the old rats had been trained in the same way and in the present procedure for 3 weeks, but with a set of shorter delays (to 8 s). Rats were maintained at 85% ($\pm$10 g) of their free-feeding weight, with water available at all times in their home cages. They were kept in a room lit by artificial light on a day–night cycle. Room temperature was maintained between 20 and 25°C. Experimental sessions were conducted daily between 0900 and 1100 h.

Apparatus

Each of the 15 Campden Instrument experimental chambers, 25 cm wide, 23 cm deep, and 20 cm high, was enclosed in a light- and sound-attenuating enclosure. Each chamber was fitted with two retractable levers situated 2.5 cm on either side of a central food dipper, which had a hinged clear Plexiglas door. Chamber illumination was provided by a 2.8-W houselight situated centrally on the chamber ceiling. Above each lever were 2.4-W lights, which were illuminated for 0.2 s each time the levers were pressed. A 2.4-W light was situated 7 cm above the Plexiglas door, and was lit during reinforcer delivery. A dipper that provided 2.5 ml of sweetened condensed milk diluted with an equal quantity of water provided reinforcement. Experimental events were controlled and recorded by individual microcomputers and associated SPIDER software and interfacing manufactured by Paul Fray Ltd.

Procedure

Daily experimental sessions consisted of 65 trials. The first trial of each session did not contribute to data analysis. Each trial began with the insertion of the sample stimulus (either the left or right lever) into the experimental chamber. Following three lever presses the lever was retracted and the retention interval initiated. The first nose poke after the completion of the retention interval was immediately followed by the insertion of the choice stimuli (both left and right levers) into the experimental chamber. A nose poke to the centrally located door of the dipper opening after the retention interval was required to prevent the rat from using positional mediating strategies. A single correct matching response (e.g., pressing the left lever when the left lever had been presented during the sample phase) retracted both levers and produced 2-s access to sweetened condensed milk. An incorrect matching response (e.g., pressing the right lever when the left lever had been presented during the sample phase) retracted both levers and resulted in a 2-s blackout period where the chamber was darkened and all responses were ineffective. Each trial was separated by a 5-s intertrial interval (ITI), which began after the 2-s access to reinforcer or the 2-s blackout period. The order of left and right sample stimuli was randomized within each session. Each type of trial was tested an equal number of times with 1-, 4-, 12- and 24-s retention intervals.

For the young rats training in the main procedure followed preliminary training in which responding on each lever was established using an autoshaping procedure. For young and old rats delayed matching-to-sample performance was established with 0.2-s delay intervals. Each rat received four sessions of training using 0.2-, 1-, 2-, and 4-s retention intervals, and three sessions using 0.2-, 1.5-, 3-, and 12-s retention intervals before baseline training using the retention intervals of 1-, 4-, 12-, and 24-s. Each rat had eight sessions of baseline training before drug testing began.

Drug Administration

AF150(S), obtained from the Institute of Biological Research, Ness Ziona, Israel, was diluted to its required concentration using double distilled water (DDW). The concentrations used were 0 (vehicle), 1, and 4 mg/ml. Dose administration occurred in the following order: 0, 1, 4, 4, 1, 0. AF150(S) was administered via intraperitoneal injections at a constant volume of 1 ml/kg 30 min before the beginning of the experimental session. Drug testing occurred on Mondays, Wednesdays, and Fridays, with baseline training occurring on the other 4 nondrug days. Each dose level was administered for two experimental sessions. By the end of drug testing each rat had received six drug sessions and six baseline sessions in total since the completion of baseline training.

Data Analysis

Total correct and error-matching responses for each retention interval were summed over the two sessions conducted for each dose level of drug for individual rats, and averaged over subjects in each group for a group analysis. Proportion correct responses was calculated by dividing the number of correct matching response by the total number of responses (correct plus error) at each retention interval for individual rats. These values were then averaged across each group to obtain group averages for each dose level.

Because the proportion-correct measure is susceptible to response bias and is bounded at 0 and 1, we also report estimates of discriminability analogous to d' of the signal detection theory. The discriminability measure does not have an upper bound and is, therefore, a more sensitive measure of performance. Discrim-

inability measures were calculated for individual rats, and averaged across rats to obtain group averages at each retention interval. To account for zeros appearing in some cells, which results in indeterminate measures, 0.5 was added to each total of every cell (23). Estimates of discriminability at each retention interval were derived from correct and error-matching responses for each of the two trial types according to Equation 1 (35).

$$\text{Log } d = 0.5\ (\log[(c1/e1) \times (c2/e2)] \quad (1)$$

The negative exponential equation (Equation 2 below) suggested by White and Harper (37) was fitted to individual and group average discriminability measures, plotted as a function of programmed retention intervals. In a previous article (30) it was argued that discriminability values for programmed and actual retention intervals fell on the same forgetting functions, and that the parameter values were virtually identical except for a small decrease in the initial discriminability parameter for programmed delays. The use of programmed retention intervals for our data analysis was therefore justified.

$$y = a \times \exp(-b\sqrt{t}) \quad (2)$$

In Equation 2, y is the measure of discriminability at retention interval t, and the parameters a and b afford independent measures of remembering (35,36). The y-intercept a describes discriminability at zero retention interval (and is referred to as "initial discriminability"), and b (the slope of the function) describes the rate of forgetting. a is related to the encoding of the sample stimuli, and is, therefore, affected by factors that disrupt attentional or perceptual processes. Factors that interfere with retrieval or rehearsal mechanisms affect rate of forgetting, b (35,36).

Proportion correct, discriminability measures, and the higher order parameters for each group were submitted to analyses of variance for repeated measures on the factor of retention interval or dose, and for the between-groups factor of age. A criterion of $p < 0.05$ was required for significance.

RESULTS

To show that the performance of young and old rats was comparable by the end of baseline training we present group-average proportion-correct responses for the two baseline sessions that immediately preceded drug testing. Figure 1 shows that performance decreased with increasing retention interval duration, $F(3, 54) = 99.96$, but did not differ between old and young rats, $F(1, 18) = 0.01$.

Figure 2 shows group-average proportion-correct responses for each dose level of AF150(S) as a function of retention interval for young (left) and old rats (right). Between group analyses revealed a significant decrease in matching accuracy as retention interval duration increased, $F(3, 54) = 89.24$. There were no significant group differences in matching accuracy, consistent with the result in Fig. 1. Within-group analyses were also performed. The administration of 1 mg/kg of AF150(S) improved the matching accuracy of young rats at the longer retention intervals, as evidenced by the significant dose by retention interval interaction, $F(3, 27) = 4.92$. Although the old rats appeared to have matched more accurately at the 4-mg/kg dose level, this was not significant. There were, however, marked individual differences in the effects of different dose levels on overall matching accuracy. All of the young rats performed more accurately at the 1-mg/kg dose level compared to the vehicle or 4-mg/kg dose level. Compared to their vehicle condition, seven old rats performed more accurately at the 4-mg/kg dose level and three

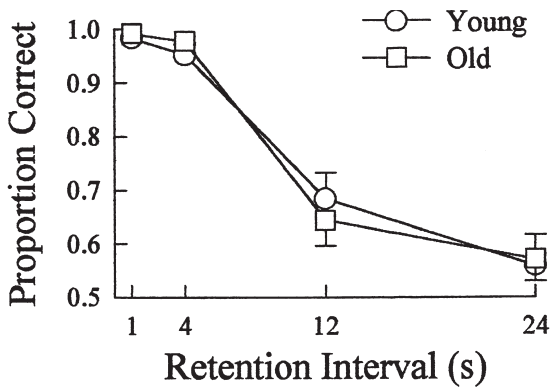

FIG. 1. Group average proportion correct responses as a function of retention interval for two sessions of baseline training for young and old rats. Vertical lines refer to standard errors of the mean.

performed more accurately at the 1-mg/kg dose level. The mean of these functions was used to determine the effect of the drug, irrespective of individual differences to the different dose levels of AF150(S). The significant delay-dependent effect of AF150(S) for the young rats is shown in Fig. 2. A comparison between drug and vehicle for the old rats revealed a significant improvement in performance following drug administration, $F(1, 9) = 17.57$, as well as a significant dose by retention interval interaction, $F(3, 27) = 3.89$, indicating that the drug influenced performance in a delay-dependent manner.

In summary, all 10 young rats and 3 old rats showed enhanced accuracy at longer delays with 1 mg/kg of AF150(S), and 7 old rats showed enhanced accuracy with the 4-mg/kg dose. Figure 3 shows group mean discriminability measures for young (left) and old rats (right) as a function of retention interval for vehicle and AF150(S) administration. The functions in Fig. 3 were based on discriminability measures for the 1-mg/kg dose for 10 young rats and 3 old rats, and for the 4-mg/kg dose for 7 old rats, that is, the most effective doses for the individuals in both groups. Between group analyses showed no age differences in matching accuracy, but there was a main effect of drug, $F(1, 18) = 8.66$, as well as a significant drug by retention interval interaction, $F(3, 54) = 4.84$.

Figure 3 also shows negative exponential fits to the discriminability measures. The intercept and rate parameters of the fitted functions give measures of initial discriminability and rate of forgetting, respectively. There were no significant age differences in either parameter, but consistent with the significant interaction between drug condition and retention interval, there was an overall lower rate of forgetting for both groups as a result of AF150(S) administration.

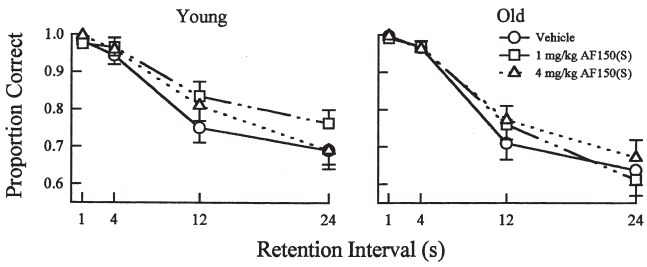

FIG. 2. Group average proportion correct responses for dose levels of AF150(S) as a function of retention interval duration for young (left) and old (right) rats. Vertical lines refer to standard errors of the mean.

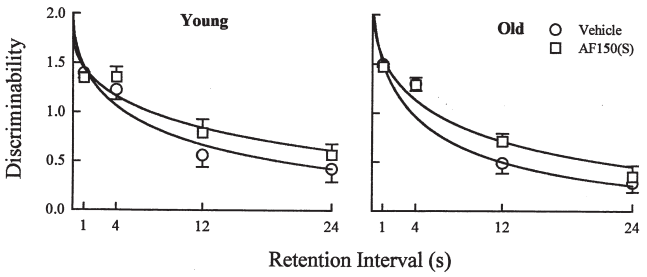

FIG. 3. Mean discriminability measures (log *d*) for vehicle and drug conditions as a function of retention interval for young (left) and old (right) rats.

DISCUSSION

We did not observe an age-related decrease in performance that has been commonly found in aged animals (2, 18,20). A number of possibilities exist as to why an age-related deficit was not evident. First, the old rats received initial training in the DMTP procedure when they were 6 months younger. It has been shown that if aged monkeys are given sufficient training on delayed matching-to-sample procedures they are able to perform at levels equal to those of younger monkeys (20). Further, Robinson, Wenk, Wiley, Lappi, and Crawley (31) compared the effects of IBO lesions to the nucleus basalis and medial septum with the selective cholinergic neurotoxin ^{192}IgG-Saproin (192-SAP) in rats. They found delay-independent changes in DNMP performance following both 192-SAP administration and IBO lesions, although performance was not significantly different from control subjects 18 weeks after surgery, despite ACh levels still being lower than those of control subjects. Second, the old rats used in this experiment were younger than those used in studies where significant age-related impairments have been found. Third, individual differences in cognitive deterioration have been found in a number of species (20). Gallagher, Burwell, and Burchinal (19) found preserved cognitive function in a significant proportion of aged rodents. Despite the failure to observe an age-related decline in matching accuracy, the cognitively enhancing effects of AF150(S) cannot be ignored.

Age-related differences in drug sensitivity were evident between young and old rats in the present study, with all 10 young rats and 3 old rats showing enhanced performance with the 1-mg/kg dose, and 7 old rats showing enhanced performance with the 4-mg/kg dose. This may be due to decreased cholinergic function reported to occur as part of the aging process. For example, a number of studies have reported decreased stimulated ACh release in basal forebrain areas in aged rodent brains compared to their younger counterparts (8,33). While only speculative, it may be the case that the higher dose level of 4 mg/kg of AF150(S) was more effective in aged rodents than the 1-mg/kg dose level because of decreased cholinergic function. Reliable age-related decreases in basal forebrain cholinergic function have been consistently found in aged rodent brains (14,15,21), and have been attributed to the decline of cognitive function seen in aged animals (2,3).

AF150(S) significantly improved the performance of both aged and young rats in a delay-dependent manner. This memory-dependent increase was supported by higher order analyses that showed a significant decrease in the rate at which information was forgotten. Although these results would add support to the cholinergic hypothesis of memory function owing to the muscarinic receptor action of AF150(S), recent literature tends to suggest that the role of cholinergic system is more complicated than first proposed. With the use of selective lesioning chemicals, such as ^{192}IgG-saporin, it has been recently suggested that the function of the cholinergic system may not be unitary (13,26). Everitt and Robbins (13) postulate that different cholinergic projections govern different psychological processes. They propose that the nucleus basalis of meynert projection is important for visual attention function; that the septohippocampal cholinergic projection is largely responsible for the modulation of short-term spatial memory; and that the diagonal band cholinergic projection is important in the utilizing response rules such as those used during conditional discrimination learning. Further, McDonald and Overmier (24) suggest that medial septal lesions produce behavioral deficits that affect delay-dependent processes, while disruption to cholinergic function in other basal forebrain areas result in delay-independent deficits. Whether, in fact, this is the case is still debated, but evidence supporting these ideas is convincing (13,26).

The enhancing properties of AF150(S) demonstrated in the current study add to previous research where AF150(S) administration successfully reversed AF64A-deficits in rats (7) and scopolamine-induced deficits in pigeons (29). The favorable properties of AF150(S), such as its high selectivity for the M1 receptor, its relatively long duration of action, and its wide therapeutic window (7) makes it an attractive option for cholinergic replacement therapy, either for patients with decreased cognitive function resulting from neurological changes that occur during normal ageing, or for patients in the early stages of AD.

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