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Short-Term Memory in the Rhesus Monkey: Effects of Dopamine Blockade via Acute Haloperidol Administration

RAYMOND T. BARTUS[1]

CNS Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research Division Ann Arbor, MI 48106

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BARTUS, R. T. *Short-term memory in the rhesus monkey: Effects of dopamine blockade via acute haloperidol administration.* PHARMAC. BIOCHEM. BEHAV. 9(3) 353–357, 1978.—The effects of dopaminergic blockade on recent or short-term memory (STM) were evaluated in test-sophisticated rhesus monkeys. Each monkey was tested under several doses of the antidopaminergic haloperidol (0.006 to 0.05 mg/kg), in an automated, delayed-response procedure. The same procedure and test apparatus had previously been used to demonstrate profound STM impairments in aged rhesus monkeys and strikingly similar deficits in young monkeys given the anticholinergic scopolamine. The results of this study do not support the notion that dopaminergic mechanisms play a critical role in primate STM. Although significant impairments in delayed-response accuracy were observed with the higher doses of haloperidol, this impairment was unrelated to the duration of the retention interval, implying a more general, non-mnemonic dysfunction. Since the qualitative nature of this deficit is dissimilar to, and not as specific as that previously found in aged rhesus monkeys (or young monkeys given scopolamine), it is suggested that age-related changes observed in the dopaminergic system are less likely to be responsible for the aged STM impairments than comparable age-related changes in the cholinergic system.

Memory, primates Dopamine, short-term memory Haloperidol, behavioral effects Primate behavior
Age-related deficits Cholinergic mechanisms, memory Dopaminergic mechanisms, memory
Cholinergic mechanisms, aging Dopaminergic mechanisms, aging Delayed response, monkeys

THERE exists growing evidence that cholinergic mechanisms play a critical role in the expression of recent or short-term memory [1, 3, 9, 10, 16, 20, 23]. Operationally, short-term memory (STM) involves the processing, storage and retrieval of information within a relatively restricted time frame. Conceptually, STM differs from long-term memory in that new learning is not necessarily involved in STM and the information that is encoded need only be temporarily retained for a short period of time before it is used and can then be disregarded.

Research concerned with the neurochemical mechanisms of STM appears to be particularly relevant to geriatric neuropharmacology, for one of the most severe and commonly reported behavioral dysfunctions reported in the elderly is a deficit in STM [7,12]. Drachman [9] has recently suggested that the specific amnestic effects that occur with cholinergic blocking agents (e.g. scopolamine) in normal adults closely mimic the STM deficit observed in geriatric patients, implying that a direct relationship may in fact exist. This concept has received independent corroborative support from laboratory studies with non-human primates. Young, healthy rhesus monkeys, tested on an automated, delayed-response procedure exhibited a specific, dose-related impairment in STM when administered low doses of scopolamine [3]. This scopolamine-induced STM impairment proved to be strikingly similar to the naturally-occurring deficit recently found in test-sophisticated, aged rhesus monkeys tested in the same apparatus and procedure [2, 4, 5].

A question of certain importance concerns how exclusive a role cholinergic mechanisms play in mediating STM. On the one hand, it has been argued that STM may represent a unique neuropharmacological process, heavily dependent upon the cholinergic transmitter system, perhaps to the exclusion of other neurotransmitters [16]. On the other hand, it has been demonstrated that inhibition of dopamine via α-methyltyrosine significantly impaired feline delayed-response performance, suggesting that dopaminergic functions may play an equally important role in the expression of STM [17,18]. Unfortunately, each conflicting line of evidence suffers certain methodological limitations, allowing equivocal, alternative interpretations to be made. For example, since neither study utilized a non-memory zero-sec delay condition, it is difficult to rule out the possibility that non-mnemonic factors may have been affected by the drugs, and that these were responsible for the behavioral impairment observed (c.f., [11]). Similarly, since multiple retention intervals were not used, it is not possible to demonstrate a

[1]Present address: CNS Research Section, Medical Research Div. of the American Cyanamid Co., Pearl River, N.Y. 10965.

relationship between the effects of the drug and the length of the retention interval. Thus, one cannot be certain that the impairments were necessarily related to events occurring during the delay, per se (i.e. memory-related events), and were, therefore, unrelated to other non-mnemonic requirements of the task [3,26]. Although both lines of evidence are certainly interesting and relevant to this issue, it is apparent that neither permit an unambiguous interpretation of the possible involvement of non-cholinergic mechanisms in STM.

Perhaps the most intriguing data related to the possibility of a non-cholinergic involvement in the age-related STM deficit are recent biochemical studies demonstrating significant changes in the dopaminergic system with aging. For example, substantial decreases in the enzyme DOPA decarboxylase, as well as in the primary metabolite of dopamine, homovanillic acid (HVA), have been reported [6, 14, 22, 24]. Furthermore, the levels of HVA have been shown to correlate with the degree of dementia better than with the actual age of the animal [13]. These data, therefore, suggest that dysfunctions in the dopaminergic system may also play an important role in the etiology of age-related behavioral changes, perhaps including STM. However, one prerequisite to this notion of a dopamine involvement, which has not been adequately settled, is whether disruption of dopaminergic functions does in fact result in qualitatively similar impairments to those observed in aged animals. The present paper was, therefore, directed toward this question. Young, healthy monkeys were tested under varying conditions of dopamine blockade using the same apparatus and procedure previously used to demonstrate specific STM impairments in aged monkeys and young monkeys given scopolamine.

METHOD

Animals

Three male and two female feral-born rhesus monkeys were used for this research. All monkeys appeared to be healthy and were estimated to be between the ages of 4 and 7 years old. They had all participated in psychopharmacological studies for a minimum of two years prior to this study and were therefore familiar with the use of the apparatus utilized in this research.

The monkeys were housed individually in animal colony facilities accredited by the American Association for Animal Laboratory Care. Their diet of Purina monkey chow and fresh fruit was given to them once per day immediately following completion of their behavioral testing. All monkeys were fed sufficient quantities of food to allow them to maintain or increase their body weight during the course of the study. Water was freely available in the home cage.

Apparatus

The apparatus used in this research was the Automated General Experimental Device (AGED), illustrated in Fig. 1. Because it has been described in detail previously [e.g., 2, 3, 5], only a brief description will be provided here. Basically, the AGED consists of a 3×3 matrix of stimulus-response (S-R) panels. Each S-R panel is hinge-mounted directly in front of a reinforcement well so that when a panel is pushed, a reed switch is activated and a reinforcement well exposed. A plastic partition, with a stimulus observation window and arm holes (see Fig. 1) separates the monkey from the S-R matrix. The stimulus observation window is equipped with a photo-cell and infrared light source to detect when the monkey is looking toward the stimuli, allowing the procedure to be subject-paced and increasing the likelihood that the animal begins processing the stimulus information at the start of each trial. Finally, a one-way viewing partition, or screen, separates the S-R matrix from the viewing partition. When this screen is backlit it appears transparent, allowing the monkey to view, but not respond to the S-R panels; when it is not backlit it is opaque, visually isolating the S-R matrix from the monkey.

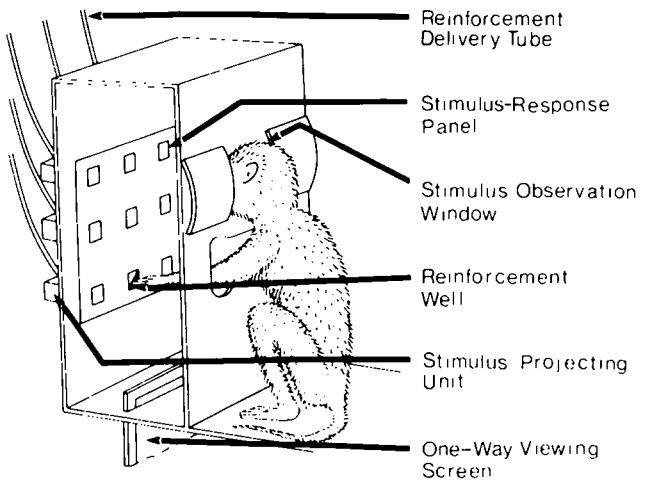

FIG. 1. Artist's conception of monkey making choice response in the Automated General Experimental Device (AGED) used in these studies. The most important features of the apparatus are labeled, with the exception of a reinforcement feeder and router mechanism (not shown) and the photocell-detecting unit located on either side of the stimulus observation window (not visible).

Color or pattern stimuli are projected onto the S-R panels by individual Series 1000 IEE displays located directly behind each reinforcement well. Automated control of the apparatus and collection of the data is accomplished using a Data General Nova 2 minicomputer, interfaced to the apparatus by BRS/LVE Interact hardware and programmed via BRS/LVE's Act III language.

Behavioral Procedure

A delayed-response procedure was used, similar to that used when studying the age-related [4,5] and scopolamine-induced STM impairments in rhesus monkeys [3]. Seventy-five trials were run per session, 5 days per week. Each trial was subject-initiated and paced, beginning as soon as the monkeys placed their face into the observation window, causing a green light to be flashed onto one of the nine S-R panels. This aspect of the procedure is important to a final interpretation of the data for it makes it reasonable to assume that the monkey was ready to begin processing the stimuli and was oriented toward them when they were presented each trial. On each trial, the stimulus was flashed two times. Each flash was 500 msec in duration, separated by a 100 msec interflash interval. If the monkeys removed their face from the observing window, the flashing was temporarily terminated until they looked into the window again. After the

stimuli flashed for two complete presentations, one of three retention intervals was initiated. These included a zero-sec control condition, a 15 sec retention interval and a longer, 30 sec retention interval. The three retention intervals were presented in a quasi-random manner so that each occurred twice every 6 trials, assuring an equal distribution within all segments of the test session. When the retention interval expired, the one-way screen was lowered and the monkey could respond by pushing one of the nine panels. If a correct response was made, the stimulus light was re-illuminated on the correct panel, a conditioned tone sounded, and a 190 mg food pellet was delivered to the exposed reinforcement well. If the response was incorrect, a buzzer sounded for 500 msec, the screen was quickly raised to obstruct further responding, and the apparatus was programmed for the next trial.

Dosing Procedure

The effects of dopamine blockade were evaluated by testing the monkeys' ability to perform this delayed-response task under varying doses of haloperidol. Haloperidol was used for this test because its mechanism of action is commonly accepted to involve highly specific blockade of dopamine receptors [8,27]. Each of the five monkeys received a total of 5 different doses (0.006 mg/kg, 0.009 mg/kg, 0.0125 mg/kg, 0.025 mg/kg and 0.05 mg/kg, suspended in methocel), according to a randomized block design, controlling for possible order effects. A maximum of two doses was given per week to each monkey, with a minimum of two days separating each administration. Non-drug control data were collected on those test days the monkeys were not administered haloperidol. All doses were administered via the intramuscular route, 30 min prior to the initiation of each test session.

RESULTS

The results were analyzed by computing the % correct responses on each of the three retention conditions under each dose of haloperidol. These results are illustrated in Fig. 2 and demonstrate a progressive drop in performance as the retention-interval duration was increased and a general deterioration in performance as the dose of haloperidol was raised. Most conspicuously absent, however, was a consistently and selectively greater effect of haloperidol as the retention duration was increased.

A 3-way analysis of variance [28] of these data confirmed these impressions. A highly reliable effect of retention interval duration was revealed, $F(2,8)=41.59$, $p<0.001$, indicating that the test situation is, in fact, sensitive to the deterioration in response accuracy that accompanies longer retention intervals. Also, a reliable effect of dose was observed, $F(5,20)=5.35$, $p<0.005$, demonstrating that increasing doses of haloperidol produce progressively greater performance impairments on this task. Finally, the dose-by-retention interval interaction did not even approach significant levels, $F(8,40)=0.75$, $p>0.10$, suggesting that little or no selective STM effect of dopamine blockade occurred as the stimulus information had to be held in memory for longer durations.

The general disruptive effects at 0.05 mg/kg were so great that all monkeys suffered some impairment on the zero-sec control condition and not a single monkey finished the complete session of 75 trials. (Even at 0.009 mg/kg, 2 of the 5 monkeys failed to complete the session with little drop in accuracy by the group.) Thus, even though clear debilitating effects on general, non-mnemonic functions were observed under haloperidol, no monkey fell to chance performance (i.e. 11.11%) on any retention interval under any dose. These effects of dopamine blockade contrast markedly with those involving cholinergic blockade. Figure 3 summarizes previously reported effects of the anticholinergic agent scopolamine when administered to monkeys of the same age group and tested in the same apparatus on the same delayed response procedure. Note that at the highest dose (0.03 mg/kg) the mean performance for the group fell to near-chance levels, while relatively little effect was obtained on the zero-sec condition. Furthermore, all monkeys completed the test session at this dose of scopolamine, and contrary to haloperidol, very little or no overt signs of the drug could be detected. This highly selective effect of low doses of scopolamine has since been replicated several times in our laboratory, in some cases with the same monkeys used in this study.

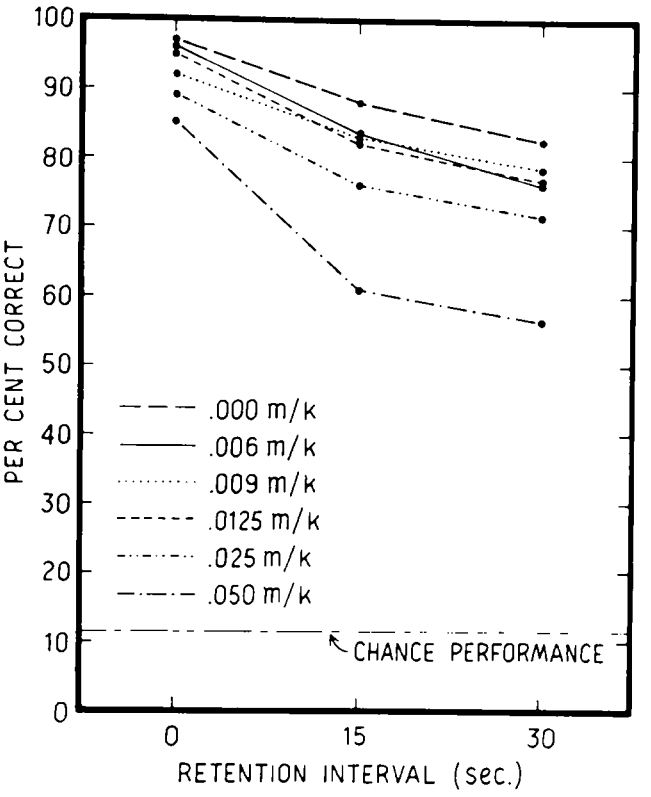

FIG. 2. Mean performance of monkeys on delayed response task under several doses of the antidopaminergic haloperidol. Note that even at the highest dose (0.05 mg/kg), performance did not drop to chance levels, even though the general disruptive effects of the drug were so great that no monkey completed the test session, and all monkeys exhibited some impairment on the zero-sec control condition.

DISCUSSION

The data reported in this paper do not support the notion that dopamine plays a direct or critical role in the expression of recent or STM in primates. Certainly, the effects of dopamine are not as specific as those previously obtained via

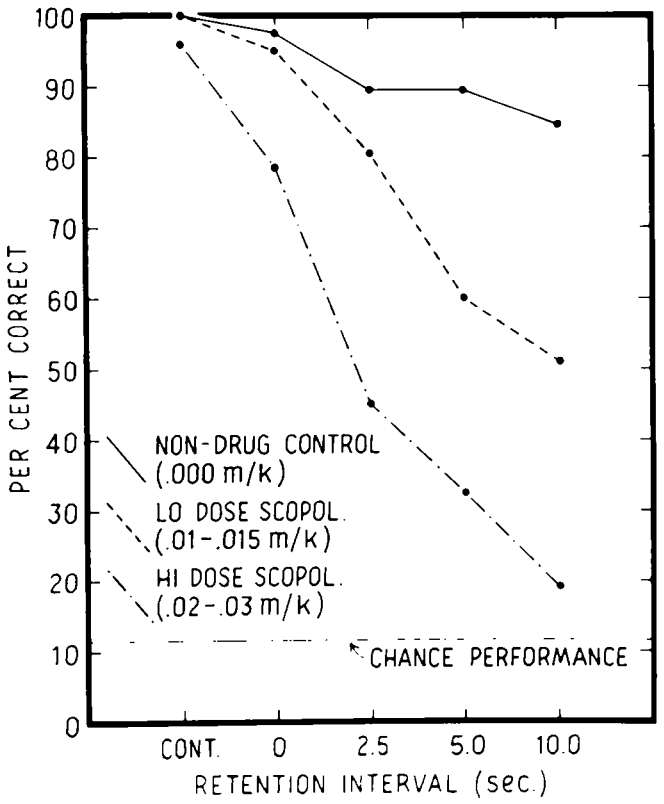

FIG. 3. Mean performance of monkeys on delayed response task under two doses of scopolamine (lo dose=0.01 to 0.015 mg/kg; hi dose=0.20 to 0.30 mg/kg) and saline control condition. The retention interval condition labeled "Cont." was a continuous information control whereby the stimulus remained on during the time the monkeys were allowed to respond, thus eliminating the need for short-term retention mechanisms. Note the progressive, dose-related impairment that occurs as the retention interval increases, with performance approaching chance levels under the higher dose. Even though performance under these doses was quite poor on the longest retention interval, all monkeys easily completed the test session.

scopolamine-induced cholinergic blockade. Contrary to the more general anti-dopaminergic impairments that occurred across all retention intervals in the present study, scopolamine produced a selective and progressively greater impairment as the information had to be held in memory for longer durations. Thus, the non-specific effects of haloperidol most likely represent some general dysfunction not directly related to the underlying neuropharmacological mechanisms responsible for STM. This conclusion that dopaminergic mechanisms are not critical for STM rests on the plausible assumption that the doses of haloperidol administered to the monkeys were, in fact, effective in blocking dopamine receptors. Considering the high degree of anti-dopaminergic specificity reported for haloperidol [8,27], together with the fact that dose-related behavioral effects were obtained (and that doses higher than 0.05 mg/kg blocked all behavioral responding), it seems reasonable to assume that a sufficient disruption in dopamine activity did occur and that this disruption was primarily responsible for the behavioral effects observed.

Kitsikis and colleagues [17,18] had previously suggested that dopamine may play an important role in STM. They found that administration of the dopamine precursor L-dopa to dopamine-deficient cats produced significant improvement in delayed-response performance. Similarly, inhibition of dopamine synthesis, via α-methyltyrosine, significantly impaired delayed-response performance in normal cats. These data clearly imply a necessary role of dopamine mechanisms in performance of the delayed response task. In fact, this finding is not inconsistent with our own data, where a general impairment in delayed response performance was also obtained with disruption of dopaminergic mechanisms. However, what was not clearly established by Kitsikis *et al.*, and where our interpretations differ, is that the major effect of dopaminergic disruption was on STM mechanisms. Their conclusion that the disruption was specifically related to STM deficits was based on the fact that visual discrimination performance was not adversely affected by the same pharmacological treatments that impaired delayed-response performance. However, because necessary behavioral controls, (such as multiple retention intervals and/or a zero-sec control condition), were not utilized in their delayed-response procedure, it is impossible to determine whether accuracy was impaired because of a failure of STM, or because of one of several other more general factors (e.g. disruption of attention, visual orientation, spatial differentiation, motivation, etc.) (c.f., [3, 11, 26]). Our data, collected in a procedure which did utilize these important controls and which also controlled for many other possible non-mnemonic, confounding factors (c.f., [3,5]), indicate that the effects of dopamine blockade are not directly related to STM mechanisms, per se. Thus, although our data are consistent with that of Kitsikis *et al.*, in that dopamine indeed may be important for successful performance in the delayed-response task, at the same time these same data are inconsistent with their interpretation that the anti-dopaminergic behavioral deficits are due to a disruption in STM mechanisms.

The data reported here also imply that the significant changes that occur in the dopaminergic system with age may be unrelated to the profound STM changes that have been observed in the clinic with geriatric humans (e.g. [7,12]) and in the laboratory with aged, non-human primates [4,5]. It seems logical that if a disruption in the dopaminergic system plays an important role in the etiology of the STM deficit seen with advanced age, selectively blocking dopaminergic activity should produce qualitatively similar deficits in young animals. The fact that such selective deficits were not produced under any of several doses of haloperidol suggests that a critical role of dopamine in the etiology of this behavioral dysfunction is unlikely. The additional fact that deficits which were qualitatively similar to those observed with aged monkeys have been consistently obtained with young, scopolamine-injected monkeys makes the notion of a necessary dopaminergic role that much more untenable.

A question which therefore becomes apparent is what role, if any, might the significant changes observed in the dopaminergic system play in aged behavior. Certainly one can speculate with some assurance that they may be related to certain motor dysfunctions known to occur with age [15, 21, 25]. The high degree of correlation and overlap in incidence of extrapyramidal parkinsonian symptoms and senility attests to the likelihood of this possibility [19]. Additionally, it is possible that dopamine may be involved in certain cognitive functions not directly related to STM. This possibility would therefore account for the apparent correlation that

exists between decreases in HVA and severity of dementia [13]. However, the disappointing lack of facilitatory cognitive effects in geriatric patients given L-dopa treatment for 6 months demonstrates that the answer to this question will not be simple [19]. Obviously, much more work needs to be done to clarify which biochemical changes in the CNS are relevant to the particular behavioral disorders that accompany old age. This work should become increasingly easier as more information is obtained regarding the role various putative CNS transmitters play in mediating the behavioral mechanisms most severely impaired. The results of this study, suggesting that dopaminergic mechanisms are not critically involved in the expression of STM, provides additional information along these lines.

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