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Reduction in distractibility with AF102B and THA in the macaque

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Abstract

Distractibility in primates may be influenced by central cholinergic systems. Two cholinomimetics, the m-1 muscarinic agonist (±)-*cis*-2-methyl-spiro(1,3-oxathiolane-5,3′)quinuclidine (AF102B, civemeline) and the cholinesterase inhibitor tetrahydroaminoacridine (THA, tacrine), were compared to vehicle controls for effects on distractibility in an automated visuospatial attention task. The task required visual pursuit of a moving target amongst distractor stimuli that acted to impair performance and was executed by seven healthy adult bonnet macaque monkeys. Task accuracy and reaction time were measured 1.5 h after systemic administration of each substance. For the seven-subject group at individually titrated best doses, accuracy increased significantly relative to vehicle for both drugs. Reaction time at best dose decreased for both drugs, but not significantly. Muscarinic agonists and cholinesterase inhibitors may reduce distractibility in primates.

Keywords: AF102B; THA; Muscarinic agonists; Cholinesterase inhibitors; Distractibility; Monkeys

1. Introduction

Increased distractibility contributes to attentional impairment in normal aging (Hoyer et al., 1979) and in psychiatric disorders such as Alzheimer's disease (Lawrence and Sahakian, 1995), schizophrenia (Addington et al., 1997), and attention deficit hyperactivity disorder (Zametkin and Ernst, 1999). Central cholinergic systems are thought to support attention in primates (Everitt and Robbins, 1997; Lawrence and Sahakian, 1995; McGaughey et al., 2000), but the relationship of acetylcholine specifically to distractibility has been less studied (Dalley et al., 2001; Sarter et al., 1996). Interest in distractibility has focussed on the nicotinic branch of the cholinergic system (Grobe et al., 1998; Hahn et al., 2002; Jessen et al., 2001; Pickworth et al., 1997; Prendergast et al., 1998; Sanberg et al., 1997; Terry et al., 2002b) with fewer investigations emphasizing muscarinic effects (Davidson et al., 1999; Egorov et al., 2002; File, 1976). The present preliminary study tested the hypothesis that acute doses of a central muscarinic agonist could improve visual attention by reducing distractibility in the macaque.

Performance on an attention task was measured following administration of the muscarinic agonist (±)-*cis*-2-methyl-spiro(1,3-oxathiolane-5,3′)quinuclidine (AF102B, civemeline). The task involved visual tracking of and selective response to a small, moving target in the presence of larger, moving visual distractors. This required the subject to ignore prominent irrelevant stimuli, an ability that declines in conditions affecting attention (Madden, 1992; Mapstone et al., 2001; Parasuraman et al., 1992). Performance on AF102B was compared to performance on the reversible cholinesterase inhibitor tetrahydroaminoacridine (THA, tacrine) and on vehicle-only controls. While AF102B acts preferentially and directly at m-1 receptors (Fisher, 2000; Fisher et al., 2002), THA indirectly affects cholinergic receptors of all types by increasing synaptic acetylcholine concentration (Chelliah et al., 1994; Håkansson, 1993). Thus, comparing effects of the two drugs may help determine if m-1 receptors contribute to cholinergically mediated changes in distractibility. Both AF102B (Fisher,

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2000; Fisher et al., 1996, 2002; Vincent and Sepinwall, 1992) and THA (Davis et al., 1992; Farlow et al., 1992; Soares and Gershon, 1995) are systemic agents that improve cognition in laboratory animals and in Alzheimer's patients. An exploratory investigation was conducted on a small group of healthy adult monkeys to determine if decreased distractibility may be one aspect of the cognitive improvement induced by these two substances.

2. Materials and methods

2.1. Subjects

Seven healthy, colony-born, adult *Macaca radiata* (bonnet macaque) monkeys weighing 4–9 kg participated in the study. One was a 6-year-old male. The other six were females aged 14, 15, 22, 26, 28, and 32 years. Ages were taken from birth records at the University of California at Davis Regional Primate Center, the source of all the animals. All monkeys were kept at the Department of Veterans Affairs Medical Center Sepulveda for several years before the study under strictly controlled conditions. All subjects had had prior behavioral training on at least one other cognitive task with the 14- and 15-year-old monkeys having somewhat more prior training than the others. Subjects exhibited no apparent cognitive or visual deficits. Systematic examination indicated that the eyes of all monkeys were free of defects such as cataracts and that all subjects were capable of picking out fine objects by eye.

2.2. Behavioral task

Monkeys carried out the attention task described below while seated alone in a primate-restraint chair in a dark, ventilated, soundproof testing chamber. At arm's length, the subject faced a 13-inch Zenith color monitor mounted in one wall of the chamber. The monitor was fitted with a Transparent Devices (Newberry Park, CA) touchscreen connected through an RS-232 serial interface to an 80486 personal computer. The computer projected stimulus images subtending 20° of visual angle at eye level on the monitor. Monkeys were trained to react to the images by touching them with the hand. Responses were sensed by the touchscreen and transmitted via the interface to the computer for recording. After correct responses only, fruit-juice rewards were delivered after a 1-s delay through a nozzle mounted next to the monkey's mouth. Overnight water restriction preceded all sessions. Subjects were observed during sessions by video camera to reduce intrusion.

Visual attention was assessed by means of a tracking task with distractors. Each task trial ran as follows: a bright, approximately 10-cm-diameter, yellow circle was centered on the screen throughout the task. At task onset, a red, 2-cm-long tadpole-like target stimulus appeared at a random spot outside the circle. Immediately, with rapid flagella-like locomotion, the target began moving randomly about the screen outside the circle at a constant speed of approximately 7.6 cm/s. At any instant, the target could penetrate the circle from any direction. After penetration, the target remained inside. The monkey's task was to touch the yellow circle within 7 s of penetration by the target ("correct response"). Not touching the screen at all during the trial was ruled an "omission." Touching the screen prematurely, or touching it outside the circle at any time, was scored as "incorrect."

Simultaneously, the monkey had to ignore the random movements of four large "distractors" on the screen. The distractors were translucent green jellyfish-like bodies approximately equal in size to the circle. They floated across the screen mostly outside, but at times also passing across the circle. Their motion was slower than that of the target (approximately 1.2 cm/s). The time point of target penetration of the circle (mean: 7.5 s; range: 0–15 s posttarget onset) and the motion patterns of the target and of the distractors varied randomly from trial to trial. The intertrial interval was 5 s (including eventual juice delivery) regardless of response. During the intertrial interval, there was nothing on the screen except the circle. For correct trials, a single 50-ms, 1-kHz tone sounded and, after a 1-s delay, a 0.1-ml fruit juice reward was delivered. Two blocks of 10 trials each were recorded in daily sessions. Accuracy was counted as the number of correct trials out of the 10 trials in a block. Single-trial reaction time was measured as the latency from target penetration of the circle to hand contact with the screen. Single-trial reaction times were then averaged across the correct trials only of each block. The sensitivity of the task to subject distractibility could be demonstrated by comparing performance between task versions with and without distractors.

2.3. Training

Chair-adapted monkeys learned to execute the task over 4–14 weeks of training (7, 14, 10, 10, 6, 12, and 4 weeks for the 6-, 14-, 15-, 22-, 26-, 28-, and 32-year-old monkeys, respectively), as evidenced by moderate to very high scores when the task was run initially at low target speed (5.7 cm/s). Concern arose that some higher-scoring subjects might encounter a performance ceiling if performance were to be raised even higher by the effects of cholinomimetics. Therefore, target speed was increased to 7.6 cm/s, resulting in moderately high accuracy for better-performing monkeys and lower accuracy for poorer performing monkeys. This intersubject performance spread left room for possible drug-mediated improvement in all monkeys. At this speed, accuracy and reaction time of each monkey then steadied to stable asymptotic values over a further 1–2 weeks of practice. Predrug baseline performance values were then collected over a final, approximately 2-week period as means of the last 12 blocks before

drug treatment. Baselines were also taken for performance on the task version without distractors.

2.4. Drugs and treatment

AF102B was synthesized as the hydrochloride salt at the Israel Institute for Biological Research and dissolved in 1 cc normal saline just before intramuscular injection. The control for AF102B was 1 cc im normal saline vehicle alone. THA (HCl salt) was obtained from Aldrich Chemical and given orally, mixed with 2 cc peanut butter vehicle. The control for THA was 2 cc peanut butter alone. Each drug or control was given daily 1.5 h before behavioral testing, a time period consistent with work in monkeys showing cortical electrophysiological or cognitive effects of AF102B and tacrine in the 45- to 120-min postadministration range (Fitten et al., 1994; O'Neill et al., 1999, 2000). Animals were checked daily for untoward reactions and unresponsiveness.

Subjects received doses of each drug in ascending series (Table 1). Drug doses were selected below levels that had been observed in pilot work to produce unresponsiveness or undesired side effects and consistent with findings in macaques of cognitive or cortical electrophysiological effects of AF102B or tacrine (Fitten et al., 1994; O'Neill et al., 1999, 2000). As untoward effects had been observed at lower doses of AF102B in older than in younger subjects, AF102B treatment was discontinued at a lower dose for the four older monkeys (Table 1). Otherwise, all monkeys were treated identically. Fewer dose increments were given for THA than for AF102B in order to reduce subject exposure to THA, an hepatotoxin (Dawson and Iversen, 1993; Fitten et al., 1990). Each dose was given five days a week with a weekend washout between successive doses. Each animal underwent one session per day (task version with distractors only) on each drug administration day during the entire sequence.

2.5. Data analyses

A subject-as-his-own-control design was used. For each monkey, accuracy and reaction time were averaged across blocks for each drug and dose condition. Data from blocks in which subjects responded to less than half the trials, i.e., blocks with >5 omissions, were excluded from analysis. Results for each dose of each drug, including vehicle-only controls were computed relative to baseline values. As considerable intersubject and interdose variation in drug response was anticipated, best-performance doses of each drug were selected for each monkey as those doses at which the greatest increase in accuracy above baseline was observed. In like manner, "best-vehicle" values were selected as the highest-accuracy performances out of the series of four vehicle-only treatments (first and second weeks of intramuscular vehicle and first and second weeks of oral vehicle).

For the baseline condition, repeated-measures analyses of covariance (ANCOVA) tested for performance differences in accuracy and in reaction time between the task version with distractors and the task version without distractors. Testing was done for rejection of the null hypothesis of no difference between the two task versions. Since four subjects were classified as "older" and three as "younger" adult monkeys, subject age in years was included as covariate. Repeated-measures ANCOVA also tested for a hypothetical main effect of the three-level factor "Drug" on each of the two performance measures relative to baseline values. The three levels of Drug were (1) best of the four vehicle-only control treatments, (2) best dose of AF102B (mean of two daily test blocks), and (3) best dose of THA (mean of two daily test blocks). Post hoc t tests then compared each of the two drugs to vehicle and the two drugs to each other. Again, age was included as covariate. To check reliability of best-dose findings, ANCOVA were repeated twice, once using AF102B and THA best-performance values from the first of the two daily testing blocks alone and once using values from the second of the two daily testing blocks alone. Criterion for significance was $P < .05$ for all tests.

Table 1
Dose sequences of drugs administered to macaques

Week	Treatment	Week	Treatment
1	1 cc im normal saline	10	washout
2	1 cc im normal saline	11	washout
3	0.1 mg/kg im AF102B	12	2 cc po peanut butter
4	0.2 mg/kg im AF102B	13	2 cc po peanut butter
5	0.4 mg/kg im AF102B	14	0.5 mg/kg po THA
6	0.6 mg/kg im AF102B	15	1.0 mg/kg po THA
7	0.9 mg/kg im AF102B[a]	16	1.5 mg/kg po THA
8	1.4 mg/kg im AF102B[a]	17	2.0 mg/kg po THA
9	2.1 mg/kg im AF102B[a]		

[a] Withheld from four oldest monkeys (22–32 years).

3. Results

3.1. Baseline performance on task with and without distractors

Table 2 lists baseline accuracy and baseline reaction time for each of the seven subjects for the task version with and for the task version without distractors. All seven monkeys had lower baseline accuracy and longer baseline reaction time on the task version with distractors than on the task version without distractors, implying that some degree of distractibility was present in all subjects. Repeated-measures ANCOVA covarying age affirmed a significant effect of task version on accuracy [$F(1,5) = 9.2$, $P < .05$] but not on reaction time [$F(1,5) = 2.8$, $P =$ ns]. Subject age did not have a significant effect on either measure. Remaining results below refer to the task version with distractors only.

3.2. Effects of vehicles and cholinomimetics on performance (task version with distractors)

Accuracy and reaction time values for all four vehicle-only treatments (two saline, two peanut butter) were close to each other and to predrug baseline values. Group mean ± S.D. best-vehicle performances were 0.2 ± 0.3 for accuracy relative to baseline (Fig. 1) and −0.07 ± 0.22 s for reaction time relative to baseline. All seven monkeys exhibited increased accuracy and three of seven exhibited decreased reaction time in response to two or more doses of AF102B. Five of seven monkeys exhibited accuracy increase and four of seven exhibited reaction time decrease at one or more doses of THA. As expected, for both drugs (more so for THA), there was considerable variation in behavioral response from dose-to-dose within subjects and in best doses between subjects.

Group mean best-dose accuracies relative to baseline were 2.2 ± 0.9 for AF102B and 1.6 ± 0.7 for THA (Fig. 1); group mean best-dose reaction times were −0.05 ± 0.7 s for AF102B and −0.61 ± 0.53 s for THA. Repeated-measures ANCOVA covarying age revealed a significant effect of drug treatment on accuracy relative to baseline [$F(2,10)=4.7$, $P<.05$]. This effect was significant for first [$F(2,10)=4.6$, $P<.05$] and for second [$F(2,10)=9.9$, $P<.01$] testing blocks. Post hoc t tests found that accuracy was significantly more improved on best dose of each of the two cholinomimetic drugs than on best vehicle (AF102B: $P<.01$, THA: $P<.0005$). These effects were significant for first (AF102B: $P<.001$, THA: $P<.0005$) and for second (AF102B: $P<.005$, THA: $P<.01$) testing blocks. Accuracy relative to baseline was significantly higher at best dose of AF102B than at best dose of THA for second testing blocks ($P<.05$) only. For reaction time relative to baseline at best dose, no significant main effect was found [$F(2,10)=0.7$, $P=$ ns]. Age did not exert significant effects on either measure.

Table 2
Baseline performances of macaques on a visual tracking task with and without distractors

Monkey	Accuracy	Accuracy	RT (s)	RT (s)
Age (years)	No distractors	With distractors	No distractors	With distractors
6	5.2 ± 2.0	4.0 ± 1.4	2.06 ± 0.90	2.71 ± 0.92
14	3.9 ± 2.5	2.1 ± 2.0	3.13 ± 0.77	3.24 ± 1.96
15	8.8 ± 2.6	7.0 ± 1.9	1.13 ± 0.93	1.34 ± 0.40
22	6.7 ± 1.2	5.8 ± 1.6	2.24 ± 0.48	2.67 ± 0.50
26	9.2 ± 1.8	7.2 ± 2.6	0.88 ± 0.10	1.26 ± 0.35
28	6.1 ± 1.4	4.2 ± 1.3	2.45 ± 0.42	3.04 ± 0.55
32	8.8 ± 0.5	7.8 ± 0.4	2.97 ± 1.26	3.44 ± 0.49
Group mean	7.0 ± 2.0	5.4 ± 2.1 *	2.12 ± 0.86	2.53 ± 0.88

Accuracies are numbers of correct trials out of 10 trials per block. Individual-subject values for both accuracy and reaction time (RT) are means ± S.D. over 12 blocks. Group values are means ± S.D. over all seven subjects.

* Accuracy with distractors significantly below accuracy without distractors [ANCOVA covarying age: $F(1,5)=9.2$, $P<.05$]. No significant difference for RT.

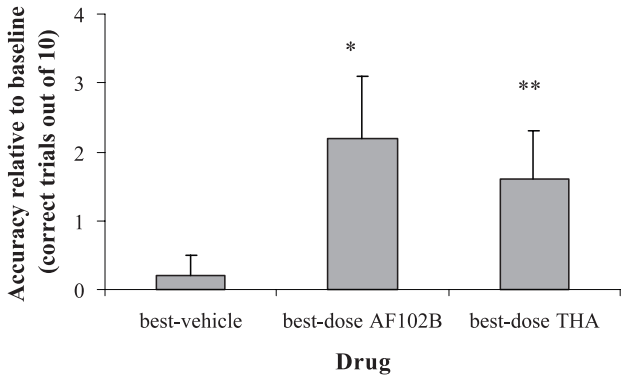

Fig. 1. Enhanced accuracy (reduced distractibility) of macaques performing a visual tracking task with distractors during systemic treatment with vehicle, m-1 muscarinic agonist (AF102B), or cholinesterase inhibitor (THA). Values are group means ± S.D. across seven subjects of individual best-dose performances relative to individual predrug baseline, expressed as numbers of correct task trials per block of 10. Best-vehicle represents the highest-accuracy performance among four separate vehicle treatments. Repeated-measures ANCOVA covarying age yielded a significant effect of Drug [$F(2,10)=4.7$, $P<.05$]. Post hoc comparisons indicated significantly greater accuracy relative to baseline on AF102B (*$P<.01$) and on THA (**$P<.0005$) than on vehicle, suggesting reduction of subject distractibility in response to cholinomimetic treatment.

3.3. Untoward effects of drug interventions

High rates of task trial omissions in behavioral pharmacological testing may signal covert toxicity (Dawson and Iversen, 1993). In the present study, rates of task trial omissions were modest both under baseline conditions and in response to cholinomimetics: Test blocks dropped due to having >5 omissions amounted to <10% of attempted blocks totaled across subjects and conditions. Emesis presented rarely as a side effect of cholinomimetics, but, on the whole, both drugs were well tolerated by all monkeys at doses tested.

4. Discussion

The effects of centrally active cholinomimetics on distractibility were examined in seven healthy adult macaques. AF102B was chosen as test agent due to its action as a partial selective m-1 muscarinic agonist and was compared to the reversible cholinesterase inhibitor THA. The major findings of this study were: (1) All monkeys attained better predrug baseline scores on the task version without distractors than on the task version with distractors; (2) for the task version with distractors, accuracy was improved 1.5 h after treatment with appropriate doses of either test drug. The first finding suggests that task performance was impaired by the presence of distractors and, hence, that the task aptly assays distractibility in primates. The second finding

suggests that acute doses of central cholinomimetics reduce distractibility in healthy primates.

Improved performance in response to AF102B supports the hypothesis that central m-1 muscarinic action contributes to distractibility reduction in primates. AF102B (Fisher, 2000; Fisher et al., 1996, 2002; Vincent and Sepinwall, 1992) and other m-1 agonists (Bartolomeo et al., 2000; Felder et al., 2000; Greenlee et al., 2001; Korcyn, 2000; Messer, 2002; Terry et al., 2002a,b) have previously been shown to improve cognition in experimental animals and human patients. This study suggests that reduction in distractibility may be one mechanism through which m-1 agonists effect cognitive improvement. Since the study design, however, did not assess effects of drug treatments on performance on the task version without distractors, it remains possible that improvements observed were mediated through muscarinic action on other aspects of attention, such as stimulus detection and response selection (Passetti et al., 2000; Robbins, 1997; Sarter and Bruno, 2000). Cognitive enhancement induced by THA and other cholinesterase inhibitors has also been demonstrated in human patients (Gauthier, 2002; Frisoni, 2001; Talesa, 2001) and in healthy adult monkeys (Bartus et al., 1982; Jackson et al., 1995; Ogura and Aigner, 1993). The present THA results suggest that reduction in distractibility may be one component of cholinesterase-induced cognitive enhancement. Such reduction in response to THA, however, may reflect action of acetylcholine on the m-1 receptor and/or on other cholinergic receptors. In particular, there is an ample literature on influences of nicotinic receptors on distractibility (Grobe et al., 1998; Hahn et al., 2002; Pickworth et al., 1997; Prendergast et al., 1998; Terry et al., 2002b). Future efforts should assess effects of m-1 agonists on performance of task versions with and without distractors, comparing these effects to those of nicotinic and other agents.

The chief limitation of this study is the small number of subjects. Replication is needed. A further limitation entails the choice of drugs. Like other agents of its class, AF102B exhibits only partial m-1 selectivity (Greenlee et al., 2001). THA is also known to exert other cholinergic effects in addition to cholinesterase inhibition (Adem et al., 1990; Håkansson, 1993). Thus, attribution of effects to m-1 agonism or to cholinesterase inhibition is uncertain and the above or similar experiments should be conducted with other, pharmacologically more selective compounds. AF102B and THA may also exert cognitive effects outside the dose ranges tested or at times longer than 1.5 h postadministration (Jackson et al., 1995; Terry et al., 2002a,b). Finally, the individual-subject best doses of AF102B and THA were selected from a series of doses tested alongside a series of vehicle treatments. A more rigorous approach for future work would be to determine individual-subject best doses in advance and subsequently to retest these best doses against vehicle.

These limitations notwithstanding, this study suggests that cholinomimetics may reduce distractibility in adult nonhuman primates. Thereby the m-1 agonist AF102B produced an equivalent or slightly greater effect than the cholinesterase inhibitor THA. Reduction of distractibility may contribute to cholinergically mediated cognitive improvements in animal models and human patients.

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