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Effects of the Alpha-2 Adrenoceptor Agonist Guanfacine on Attention and Working Memory in Aged Non-Human Primates

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Abstract

Alpha-2 adrenergic receptors are potential targets for ameliorating cognitive deficits associated with aging as well as certain pathologies such as attention deficit disorder, schizophrenia, and Parkinson's disease. Although the alpha-2 agonist guanfacine has been reported to improve working memory in aged primates, it has been difficult to assess the extent to which these improvements may be related to drug effects on attention and/or memory processes involved in task performance. The present study investigated effects of guanfacine on specific attention and memory tasks in aged monkeys. Four Rhesus monkeys (18–21 years old) performed a sustained attention (continuous performance) task and spatial working memory task (self-ordered spatial search) that has minimal demands on attention. Effects of a low (0.0015mg/kg) and high (0.5 mg/kg) dose of guanfacine were examined. Low dose guanfacine improved performance on the attention task (i.e., decreased omission errors by $50.8 \pm 4.3\%$ ($p = 0.001$) without an effect on commission errors) but failed to improve performance on the spatial working memory task. The high dose of guanfacine had no effects on either task. Guanfacine may have a preferential effect on some aspects of attention in normal aged monkeys and in doing so may also improve performance on other tasks, including some working memory tasks that have relatively high attention demands.

Keywords

aging; spatial memory; attention; primate; noradrenergic

Introduction

The noradrenergic system, and specifically, alpha-2 adrenergic receptors, play an important role in cognitive functions such as memory, learning and attention (Arnsten et al. 1998) and this is particularly true in the prefrontal cortex (PFC) (Arnsten 2006). Pharmacological manipulation of this system for improvement of attention and memory has received considerable attention (for a review, see Coull 1994). Alpha-2 adrenergic receptor agonists have been suggested as potential therapeutics for a variety of cognitive disorders including “normal” age-related cognitive decline, pathological memory disorders and attention deficit disorder (Arnsten et al. 2007). Beneficial effects of alpha-2 adrenergic agonists on attention and working memory have been reported in a variety of animal models (Arnsten and Cai 1993; Arnsten and Contant 1992; Arnsten and Goldman-Rakic 1990; Buccafusco et al.

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2009; Jentsch and Anzivino 2004; O'Neill et al. 2000), with studies on aged non-human primates receiving a considerable amount attention. In particular, the noradrenergic agonists guanfacine and clonidine have been proposed as potential therapeutic agents for treating age-related cognitive problems as well as certain conditions (ex., ADHD, schizophrenia, Parkinson's disease) that present with cognitive disturbances (Cannon et al. 2009; Friedman et al. 2004; Palumbo et al. 2008; Riekkinen et al. 1999a; Riekkinen et al. 1999b; Riekkinen and Riekkinen 1999).

Although the effects of noradrenergic agonists on cognition have been studied in aged non-human primates, the effectiveness of these drugs on attention and memory *per se* is somewhat difficult to interpret since most studies have utilized cognitive testing paradigms that significantly involve both cognitive processes. For example, both clonidine and guanfacine improve "memory" of aged rhesus monkeys performing a delayed response (DR) task (Arnsten et al. 1988). However, in this task, both attention (e.g. observing the experimenter as the cue is being presented for a short period of time) and memory (remembering where the cue was presented over increasingly long delay periods) are necessary in order to perform the task correctly. Improvement of delayed response performance has also recently been shown after administration of methylphenidate or atomoxetine, with effects attributed to indirect stimulation of alpha-2 adrenoceptors and D1 dopamine receptors in the prefrontal cortex (Gamo et al. 2010).

The effects of clonidine and guanfacine have also been assessed on a variant of the DR task in which the intra-trial delay period was purposely kept short so as to minimize memory demands of the task and distracters were presented during some of the delay intervals (Arnsten and Contant 1992). The presence of distracters disrupted the performance of aged monkeys on trials with distracters as well as on remaining non-distracter (interference) trials. After administration of clonidine or guanfacine, performance was not impaired on distracter or non-distracter trials, suggesting that these drugs have a positive effect on attention but may also be able to protect memory from irrelevant stimulation (Arnsten and Contant 1992). O'Neil et al. (2000), examined the effect of guanfacine on attention using a delayed matching-to-sample task, a one-target visual tracking task (measure of focused attention) and a two-target visual tracking task (measure of divided attention), each employing distracting stimuli. Guanfacine improved performance of all 3 tasks, suggesting that guanfacine may enhance attention and reduce distractibility. It was not possible to determine, from the data presented, whether an effect on memory could also be inferred. Thus, noradrenergic manipulation may improve performance of aged animals in tasks aimed at assessing working memory but may do so preferentially in tasks that require both attentional and mnemonic functions.

The present study was conducted to assess the extent to which positive effects of guanfacine on cognition in aged primates could be detected using tasks specifically designed to primarily and preferentially assess attention or spatial working memory. In this work, we used a Continuous Performance Task to assess the ability to maintain an attentional focus (i.e., a consistent focus on some continuous activity or stimuli) with no dependence on working memory (i.e., each successive trial on the CPT has no relation to a previous trial and does not require holding and utilizing prior information in which to base a decision concerning new information). We also used a Self-Ordered Spatial Search Task to assess spatial working memory (i.e., the ability to retain spatial information and to manipulate remembered items to discriminate information in a trial from information presented earlier in the testing; the self-ordered component also assesses heuristic (experience-based) strategy).

Materials and methods

Subjects

This study utilized four aged male rhesus monkeys (*M. mulatta*), approximately 18 to 21 years old at the onset of the study. Animals were maintained on a food restriction schedule (which did not change throughout the study) optimized per animal to maintain stable performance and had access to water *ad libitum*. The animals used had comparable characteristics in terms of their ability to learn and perform the tasks and were “normal” aged monkeys that had not been part of other pharmacological projects prior to this study. All procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Thomas Jefferson University Institutional Animal Care and Use Committee.

Cognitive Testing

For training and testing, animals were transferred (using a specially designed transport cage) from their home cage to a testing cage located in a quiet room away from the main colony. Personnel operating the computer-controlled tasks did so remotely and could not be seen by the animal during testing. A test panel consisting of a touch sensitive computer display, a speaker for delivery of reinforcing sound and a reward delivery system was attached to the testing cage. Prior to initiating a testing session, house lights were dimmed and white noise provided. Animals were typically trained two to three times per week on each task. Two tasks, one selective for attention and one selective for spatial working memory were used.

A) Continuous Performance Task (CPT)—This task was a modified version of a continuous performance task previously used in non-human primates (Golub et al. 2005) and was used to assess sustained attention (vigilance) as well as provide information regarding inattention and impulsivity. On this task, stimuli were colored rectangles (yellow, black, or white) that appeared in the middle of the screen. One of the three rectangles (yellow) was the target and the animal had to touch this target as quickly as possible when it appeared on the screen in order to receive a reward. If he touched a non-target rectangle (white or black) no reward was given. Training continued until an asymptotic performance level was reached on sessions in which 30 percent of the trials were target. The stimuli were presented for 1 sec., with an inter-trial interval of 1 sec. A total of 200 trials made up a daily testing session. The measures recorded were: 1) commission errors (number of touches to non-targets); 2) omission errors (number of times target appears but is not touched); and 3) reaction time (time between appearance and touch of target).

B) Self-Ordered Spatial Search (SOSS)—The SOSS task (designed to study spatial working memory) was modeled after a similar task in the Cambridge Neuropsychological Test Automated Battery (Monkey CANTAB Cognitive Testing System, Lafayette Instrument, Lafayette, IN) and used previously in non-human primates (Weed et al. 1999). The task has several levels of difficulty. At the simplest level, 2 blue squares appear on the screen, in no obvious pattern, against a white background. The screen has 8 possible locations in which a square can appear. The animal must then select (touch) each box in turn without revisiting a box once it has been touched. In order to perform this task, the animal touches one of the boxes (within 20 seconds of appearance) causing it to briefly (100 msec.) turn red. Both boxes disappear from the screen for 2 seconds and then reappear in the same locations as before. The animal needs to remember which box it previously touched and now touch the other one. If the animal touches the box that previously was not touched, it receives a reward; if it touches the same box it previously touched, it does not turn red, there is no reward given and the boxes disappear from the screen for a 20 second time-out period. If the animal touches all of the boxes in a sequence without a repetition, the trial is labeled

“correct”. If the animal returns to a box that has already been touched it is recorded as a repeat search error. The number of these errors is recorded. Once an asymptotic level of performance is achieved at this first level of difficulty and is stable for several days, the next level of the task, in which three squares are utilized, is introduced to the animal. A daily session then consists of a set of trials (sequences) with 2 squares and a set of trials with 3 squares. Again, after an asymptotic level of performance is achieved at the 3 square level of difficulty and is stable for several days, the next level of the task, in which four squares are utilized, is introduced. Training continued until performance stabilized and each monkey’s normal limits of spatial working memory could be determined. Sessions consisted of 30 trials divided into repeating blocks by trial type.

Drug administration

After stable baseline performance was established, guanfacine and saline (control) administration sessions began. The doses of guanfacine used (0.0015mg/kg and 0.5 mg/kg given i.m. 120 minutes prior to testing) were the same as those previously showing significant effects of guanfacine on cognition in aged monkeys (Arnsten et al. 1988; Arnsten and Contant 1992; Franowicz and Arnsten 1998; O’Neill et al. 2000; Rama et al. 1996) and which did not produce sedation. Guanfacine (Sigma-Aldrich, Inc.) was diluted in sterile saline immediately prior to each drug testing session in a constant volume of 0.5 ml saline. Vehicle testing session used a 0.5 ml volume of saline administered 120 minutes prior to onset of testing. Guanfacine was administered in ascending doses and there was a minimum 7-day washout between drug trials. Saline control testing sessions were performed prior to drug testing sessions to verify baseline performance.

To assess the specificity of any response to guanfacine, the alpha-2 noradrenergic antagonist idazoxan (Sigma-Aldrich, Inc.) was administered in conjunction with guanfacine on some trials. In these instances, idazoxan (0.1mg/kg; i.m.) was administered immediately prior to administration of guanfacine

Statistical analysis

Descriptive data are shown as mean $\pm$ standard error of the mean (SEM). Due to inter-individual differences in baseline levels of performance, data were normalized as percent change from baseline for both tasks used. Animals served as their own controls, and statistical analyses used repeated measures one-way analysis of variance followed by post hoc comparisons using Bonferroni’s Multiple Comparison Test to compare saline control and drug administration data (GraphPad Prism). Differences between means were considered significant at the $p < 0.05$ level (2-sided).

Results

In the present study, guanfacine produced no significant sedation effects and no adverse or gross behavioral side effects.

Continuous Performance Task

Under vehicle control conditions, the performance of aged animals was marked by a mix of omission and commission errors. The number of commission errors however, was low (2.1 ± 0.85) and more consistent across animals compared to the number of omission errors (16.1 ± 7.7). The time taken by the animals to respond to the target stimulus was 588 ± 62 msec and was relatively consistent across animals.

Guanfacine administration had a significant effect on the number of omission errors produced ($F(3,11) = 23.54$, $p = 0.0014$). Administration of the low dose of guanfacine

decreased the number of omission errors by $50.7 \pm 4.4\%$ (compared to vehicle) ($t = 4.80$, $p < 0.01$). Administration of the higher dose of guanfacine produced no significant effects on omission errors ($t = 1.84$, $p > 0.05$) (Figure 1A).

There were no significant effects of guanfacine at either dose on the number of commission errors ($F(3,11) = 0.19$, $p = 0.83$). Neither dose of guanfacine had a significant effect on reaction time when compared to vehicle sessions (588 ± 62 msec. vs. 599 ± 63 msec. vs. 677 ± 43 msec. for vehicle, guanfacine low dose, and guanfacine high dose, respectively, ($F(3,11) = 0.74$, $p = 0.51$) (Figure 1B).

The co-administration of the noradrenergic antagonist idazoxan (0.1mg/kg) in conjunction with the low, effective dose of guanfacine (i.e., 0.0015mg/kg) abolished the positive effect of guanfacine on omission errors and resulted in a level of performance not significantly different from that observed following vehicle administration ($p = 0.297$) (Figure 1A).

Self-Ordered Spatial Search Task

There was an effect of task difficulty on baseline performance ($F(2,11) = 10.76$, $p = 0.004$). After reaching a stable level of performance, aged monkeys performed the task well at the easiest level (2 squares) ($89.2 \pm 2.8\%$ sequences completed). Performance decreased at the 3 squares level ($56.7 \pm 7.4\%$ sequence completed) and at the 4 squares level ($44.1 \pm 9.4\%$ sequence completed). Animals performed significantly worse at the 3 ($p < 0.05$) and 4 squares levels ($p < 0.01$) than at the 2 squares level (Figure 2A). One animal failed to complete any sequences at the most difficult level of the task, with its behavior marked by numerous omission errors. The data from this animal were removed from baseline and vehicle / drug testing sessions only for the 4 squares condition.

Administration of guanfacine (0.0015mg/kg or 0.5 mg/kg) had no significant effects on performance at the 2 squares level ($p = 0.18$, $p = 0.59$, respectively), the 3 squares level ($p = 0.43$, $p = 0.22$, respectively) or the 4 squares level of the task ($p = 0.15$, $p = 0.31$, respectively) (Figure 2B).

Discussion

The present study evaluated the effect of the alpha-2 noradrenergic agonist guanfacine on aged primates trained to perform an attention task with no working memory component (e.g. CPT) and a spatial working memory task with minimal attentional demands (e.g., SOSS task). Our results show that guanfacine improved one measure of sustained attention (i.e., decreased omission errors) but not a measure of impulsivity (i.e., commission errors). An effect on sustained or selective attention (omissions) without an effect on impulsivity (commissions) is not completely unexpected since these activities may involve different neural circuits. Guanfacine also had no effect on working memory as assessed by the SOSS task.

These results differ somewhat from results of other studies that examined the effects of guanfacine on cognition in aged non-human primates (Arnsten et al. 1988; Arnsten and Goldman-Rakic 1990; Buccafusco et al. 2009; Franowicz and Arnsten 1998; Rama et al. 1996). This discrepancy may be related to differences in the nature of the tasks used previously and the current tasks, and the type of cognitive processes involved in performance of these tasks. For example, in one study (Arnsten et al. 1988), guanfacine had a significant and robust effect on performance of aged animals on a variable delayed response task. In that task, both attention and short-term memory are involved as the animal must first pay attention to the stimulus presented to him prior to storing information on the location of the stimulus in memory. Accurate delayed response performance requires that

the animal pay attention to the baiting of the possible reward location and memory of the location of the baited most recently and the ability to discriminate the current trial from information presented earlier in the testing (Gallagher & Rapp, 1997). That guanfacine improved overall performance on this task could be explained, at least partially, by an effect on the attentional component of the task. Although it is possible that guanfacine may also have had beneficial effects on memory, this is difficult to evaluate as the data presented did not differentiate between performance at short versus long delay trials. We have previously shown that improving performance on the attentional component of a variable delayed response task can improve overall performance without necessarily having a direct effect on memory (Decamp and Schneider 2009; Decamp et al. 2004). When aged animals were tested using a modified variable delayed response task in which the demand on memory was kept low and distracters were presented during some trials, both clonidine and guanfacine decreased the effect of distraction on performance. In the current study, guanfacine decreased the number of omission errors on the continuous performance task suggesting enhanced vigilance or sustained attention and decreased distractibility. The continuous performance task assesses the maintenance of attention for infrequent but critical events (that occur at random intervals) over sustained periods of time and as such, has no working memory component.

While guanfacine appears to have an effect on at least some components of attention in aged non-human primates, the effects of this drug on memory are less clear. When aged animals performed a non-spatial working memory (delayed non-match-to-sample (DNMS)) task with a high demand on memory processes and minimal attentional demands, guanfacine, at doses that produced improved performance on a delayed response task with attentional and memory demands, had minimal effects (Arnsten and Goldman-Rakic 1990). It was suggested that the lack of efficacy of noradrenergic agonists in aged monkeys performing this non-spatial working memory task could be related either to a ceiling effect (i.e., the animals performed this task at a level that could not be significantly improved) or to a preference for these drugs to improve working memory for spatial material (Arnsten and Goldman-Rakic 1990). In the current study, guanfacine did not improve performance on a spatial working memory task (the SOSS task) that has minimal attentional demands. The task requires monitoring of self-generated choices with performance of the task entirely dependent on memory of the visual stimuli, their locations, and previous responses and is not dependent on general attentional functioning (Owen et al. 1990; Clark et al. 2007; Chamberlain et al. 2011). The lack of effect of guanfacine on the SOSS task was not due to a ceiling effect as performance in the SOSS task, particularly at the medium and most difficult levels, was low enough to be able to observe guanfacine-related improvement if it occurred. It may be that guanfacine, in aged animals and at the doses used, may preferentially improve attention without a substantial effect on memory processes. However, an effect of alpha-2 agonists on working memory in other situations and clinical conditions cannot be dismissed (see Ramos and Arnsten 2007 for review).

Recent clinical data also argue in favor of an effect of noradrenergic modulation of attention as presently observed. Some studies have reported guanfacine-related improvements in working memory, planning and paired associates learning tasks in healthy adults (Jakala et al. 1999a; Jakala et al. 1999b) while in other studies of central executive functions and memory in healthy volunteers (using a human equivalent of the SOSS task used in the current study), guanfacine had no effect on spatial working memory performance (Muller et al. 2005). Interestingly, guanfacine also had no effects on other forms of memory (e.g., declarative memory) or on a measure of central executive functioning (e.g., attentional set shifting). It is possible that the positive effects observed in the Jakala et al. studies could be related to insufficient control of the attentional aspects of the tasks. In a study that assessed sustained attention and divided attention in adults with attentional deficit hyperactivity

disorder (ADHD), guanfacine improved the measure of sustained attention but not a measure of divided attention (Taylor and Russo 2001). Guanfacine has also improved performance of subjects with ADHD on Connors CPT (Scahill et al. 2001).

In conclusion, our results suggest that in aged non-human primates, noradrenergic manipulation with an alpha-2 agonist may improve some aspects of attention and in doing so may also improves performance on other tasks (including some working memory tasks) that have relatively high attention demands. Thus, guanfacine (and possibly other alpha-2 agonists) may provide benefit for treatment of cognitive dysfunction and improvement of activities of daily living that depend upon optimal attentional functioning.

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Figure 1.

The effects of guanfacine on omission and commission errors (A) and reaction time (B) on the continuous performance task. Results represent mean percent change from baseline ($\pm$ SEM) (A) and mean reaction time ($\pm$ SEM) expressed in milliseconds (B). *Significantly different from baseline performance at $p < 0.01$

Figure 2.

The effects of guanfacine on performance of the self-ordered spatial search task (SOSS). Results represent (A) mean number ($\pm$ SEM) of sequences completed per level of difficulty on the SOSS task and (B) mean percent change from baseline performance ($\pm$ SEM) per level of difficulty at the SOSS task. *, ^ Significantly different from the 2 squares level of difficulty at * $p < 0.05$, ^ $p = 0.01$