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The Alpha-1 Adrenergic Agonist, Cirazoline, Impairs Spatial Working Memory Performance in Aged Monkeys

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ARNSTEN, A. F. T. AND J. D. JENTSCH. *The alpha-1 adrenergic agonist, cirazoline, impairs spatial working memory performance in aged monkeys.* PHARMACOL BIOCHEM BEHAV **58**(1) 55–59, 1997.—The alpha-1 adrenergic agonist, cirazoline, was examined for effects on spatial working memory performance in aged rhesus monkeys. Cirazoline has additional high affinity for imidazoline receptors and has good brain penetrance when administered systemically. Spatial working memory was assessed using the variable delayed response task, a test dependent upon prefrontal cortical function in monkeys. Low doses of cirazoline (0.00001–0.001 mg/kg) impaired delayed response performance significantly. This impairment did not appear to result from nonspecific changes in behavior, because cirazoline had no significant effect on performance of control trials where the delay was "0" s, and had no significant effect on behavioral ratings. Impairment was reversed by pretreatment with the alpha-1 adrenergic antagonist, prazosin, consistent with drug actions at alpha-1 adrenergic receptors. In contrast, preliminary data suggest that higher cirazoline doses (0.001–0.01 mg/kg) occasionally produced improved performance that was not reversed by prazosin, but rather, by the imidazoline/alpha-2 adrenergic antagonist, idazoxan. The finding that alpha-1 adrenergic receptor stimulation impairs spatial working memory performance complements previous research demonstrating that alpha-2 adrenergic receptor stimulation improves working memory, and suggests that norepinephrine may have opposing actions at alpha-1 vs. alpha-2 receptors in the prefrontal cortex as it does in the hypothalamus and thalamus. © 1997 Elsevier Science Inc.

Alpha-1 adrenergic receptors Alpha-2 adrenergic receptors Imidazoline Norepinephrine Cirazoline
Prefrontal cortex Aging Memory Prazosin Idazoxan Monkeys Delayed response task

A PRIMARY function of the prefrontal cortex (PFC) is to guide behavior by working memory. For more than 60 years, it has been appreciated that lesions to the dorsolateral PFC in monkeys produce profound and lasting deficits on spatial working memory tasks such as delayed response [(20), reviewed in (18)]. Lesions to the PFC produce marked spatial working memory impairments even at short delays (e.g., 5 s), whereas performance is preserved following no delay control conditions [e.g., (17)].

Catecholamines have a major influence on PFC working memory function: 6-hydroxydopamine lesions of the dorsolateral PFC that produced marked depletion of both dopamine (DA) and norepinephrine (NE) produced spatial working memory deficits as pronounced as those induced by ablation of the same region (13). Although most research has focused on the role of DA in the PFC [e.g., (13,28)], additional research has also demonstrated that NE has important beneficial actions in the PFC through actions at alpha-2 adrenergic receptors [(6,23), reviewed in (10)]. The beneficial effects of alpha-2 agonists such as clonidine are amplified in aged monkeys with naturally occurring NE depletion (1,6), and in young monkeys with experimentally induced NE depletion (6,15), consistent with drug actions at receptors postsynaptic to NE terminals. These actions exhibit an alpha-2A receptor subtype pharmacological profile (2,8,10).

In contrast, little is known about alpha-1 adrenergic influences on the spatial working memory functions of PFC. The alpha-1 adrenergic antagonist, prazosin, does not impair working memory following systemic administration in aged monkeys (6) or intra-PFC infusion in young monkeys (23), suggesting that tonic alpha-1 receptor stimulation is not critical to PFC function. However, the effects of increased alpha-1 receptor

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stimulation with alpha-1 agonist administration have not been examined, in part due to the paucity of alpha-1 adrenergic agonists that cross the blood/brain barrier. Recently, the alpha-1 adrenergic agonist, cirazoline (2-(2′-cyclopropylphenoxymethyl)-imidazoline), has become available for experimental analysis. Although cirazoline has high affinity for imidazoline as well as alpha-1 adrenergic receptors (12,27), it is purported to have good brain penetrance (16). For example, cirazoline has been shown to decrease eating in rodents following either systemic administration (0.05–0.4 mg/kg), or infusion into the paraventricular nucleus of the hypothalamus [3–24 nM; (16)]. The current study examined the effects of cirazoline on spatial working memory performance in aged monkeys.

METHOD

Subjects

Five aged female rhesus monkeys (*Macaca mulatta*) were used in this study; however, one animal died before the dose/response curve was completed and thus only the complete dose/response curves from the remaining four animals are reported. The monkey's death was unrelated to cirazoline administration. The monkeys ranged in age from about 20 to 35 years. Because actual birth dates were unavailable for most monkeys, ages were estimated on the basis of prior breeding and behavioral testing records, dental records, and general appearance. Rhesus monkeys in captivity have been reported to live 20–25 years and occasionally longer (21,30). All animals were housed individually under standard laboratory conditions. All monkeys had participated in at least one of several previous studies of monoaminergic receptor compounds (3–5,8,9).

Cognitive Testing

Cognitive testing was conducted in a Wisconsin General Test Apparatus (WGTA) in a sound-attenuating room. Background masking noise (60 dB, wideband) was used to minimize auditory distractions. Animals were always tested at the same time of day immediately prior to feeding. Highly palatable food rewards (e.g., peanuts, raisins, or chocolate chips) were utilized during testing to minimize the need for dietary regulation. Using these conditions, no problems with motivation were evident.

The monkeys had been trained previously on the 2-well delayed response task. During delayed response, the animal watched as the experimenter baited one of two foodwells. The foodwells were then covered with identical cardboard plaques, and an opaque screen was lowered between the animal and the test tray for a specified delay. At the end of this delay, the screen was raised and the animal was allowed to respond. Reward was distributed quasi-randomly between the left and right wells over the 30 trials that made up a daily test session.

The monkeys were tested on the variable delayed response task, in which the delays varied between less than 1 s ("0" s) and the temporal interval that produced performance near chance levels for each animal within a session. Five different delay lengths were distributed quasirandomly over the 30 trials that made up a single test session. For example, the range of delays for aged monkey #124 was "0", 4, 8, 12, and 16 s. All monkeys performed near perfectly at "0" s and exhibited increasing difficulty with progressively longer delays, a pattern consistent with working memory impairment. Delays were adjusted until the animals showed stable baseline performance of approximately 67% correct (i.e., between 18 and 22 trials correct from a possible 30 trials). The aged monkeys were tested twice a week, with 3–4 days separating test sessions (e.g., Mondays and Thursdays). The experimenter testing the animal was unaware of the drug treatment conditions.

Behavioral Assessment

Changes in behavior were evaluated during cognitive testing by an experimenter who was familiar with the animal, but was "blind" to the drug treatment conditions. Sedation and agitation were rated using a nine-point scale, where 0 = normal level of arousal, I = quieter than usual, II = sedated (drooping eyelids, slowed movements), III = intermittent sleeping, and IV = too sedated to finish testing; −I = more alert than usual, −II = slight agitation, but not sufficient to disrupt testing, −III = agitation disrupting testing, and −IV = too agitated to test. Aggression was rated using a seven-point scale, where 0 = normal level of aggression, −I = slightly more aggressive, −II = moderately more aggressive, and −III = extremely aggressive; I = slightly more docile, II = moderately more docile, and III = very docile. The animals were also observed for changes in gross motor function (e.g., circling) and for changes in pallor indicative of altered blood pressure.

Drug Administration

Cirazoline hydrochloride (0.00001–0.01 mg/kg, IM) was dissolved in sterile saline under aseptic conditions and administered in a volume of 0.1 ml/kg 30 min prior to testing. Prazosin was fed to the animals in a chocolate rice cereal vehicle 1 h before testing; the 0.1 mg/kg (PO) dose used to challenge the cirazoline response had been shown to previously have no effects on performance by itself (6). All drug effects were compared with performance following matched vehicle controls. Drug administration occurred only after an animal had returned to baseline performance for two consecutive test sessions. Therefore, all washout periods between drug injections were at least 10 days. When a dose of cirazoline was identified that either impaired or improved delayed response performance beyond baseline performance, the dose was repeated to determine the replicability of the drug effect. Replicable cirazoline effects were then challenged with prazosin to assess the contribution of alpha-1 receptor mechanisms.

Cirazoline was generously provided by Synthelabo Recherche (Bagneux, France); idazoxan was purchased from Research Biochemicals Inc (Natick, MA, USA); prazosin was purchased from Sigma Co. (St. Louis, MO, USA).

Data Analysis

Delayed-response performance on drug was compared with matched vehicle (saline) control performance for the same week. Because the animals served as their own controls, statistical analyses employed repeated measures designs (1-ANOVA-R, 2-ANOVA-R, T-dep). The effect of cirazoline on delayed response performance following no delay vs. delay conditions was examined using a 2-way ANOVA with repeated measures, with factors of drug and delay, followed by post-hoc tests to examine drug effects following no delay vs. delay conditions. This analysis used both the original response to drug and subsequent replications. Paired *t*-tests, (T-dep) were used to assess the effects of antagonist pretreatment. Behavioral rating data in the aged animals were assessed using a nonparametric analysis (Wilcoxon). Statistical analyses were con-

ducted on a Macintosh LC III computer using a statistics package (Systat).

RESULTS

The effects of cirazoline on delayed response performance in the four aged monkeys are illustrated in Fig. 1. In general, low doses impaired performance, whereas higher doses had no effect or improved performance. Although all animals showed impairment following a dose of cirazoline between 0.00001 and 0.001 mg/kg, not all animals were impaired by the same dose. Thus, an 1-ANOVA-R on cirazoline dose failed to reach significance with this small number of animals, $F(4,12) = 1.34$, $p = 0.31$. There was a significant linear component to the dose/response curve (polynomial contrasts: 1° $F(1,3) = 10.56$, $p = 0.047$).

For each aged monkey, a low dose of cirazoline (0.00001–0.001 mg/kg) was identified that produced replicable impairment in delayed response performance. The qualitative nature of the impairment was analyzed further to determine whether cirazoline impaired performance following "0" s delay control conditions (i.e., evidence of nonspecific effects on performance), or whether the impairment was selective for delay conditions. A 2-ANOVA-R with factors of cirazoline and delay showed a significant effect of cirazoline, $F(1,7) = 9.62$, $p = 0.017$, a significant effect of delay, $F(1,7) = 38.44$, $p < 0.0001$, and a trend for a cirazoline by delay interaction, $F(1,7) = 0.09$. The impairment induced by cirazoline appeared to result from cognitive impairment rather than nonspecific changes in performance, because cirazoline had no significant effect on performance following the "0" s delays [Fig. 2; cirazoline vs. saline: $F(1,7) = 2.3$, $p = 0.17$]. In contrast, performance was significantly impaired on trials with delays greater than 0 s [Fig. 2; cirazoline vs. saline: $F(1,7) = 8.53$, $p = 0.022$].

The doses of cirazoline that impaired delayed response performance also had little effect on behavioral ratings: median sedation score rating following saline was 0 (all scores 0); median sedation score rating following cirazoline was 0 (a single score each of −2 and 1, all other scores 0; Wilcoxon saline vs. cirazoline $p = 0.65$). No changes in aggression were noted following cirazoline treatment (all scores 0). Because cirazoline (0.05–0.4 mg/kg) can decrease eating in rodents (16), changes in motivation following cirazoline treatment were of particular interest. Decreased interest in food rewards was observed only once following cirazoline treatment in monkey #499; delayed response performance was not impaired during this session (no. trials correct, saline: 19/30; no. trials correct, cirazoline (0.01 mg/kg): 19/30).

The impairment in delayed response performance produced by low-dose cirazoline administration was reversed by pretreatment with 0.1 mg/kg of the alpha-1 adrenergic antagonist, prazosin (Fig. 3; vehicle+cirazoline vs. prazosin+cirazoline: T-dep = 5.22, df = 3, $p = 0.01$). These results are consistent with an alpha-1 adrenergic mechanism underlying the impairment in delayed response performance.

Delayed response deficits were generally not evident following higher cirazoline doses (0.001–0.01 mg/kg; Fig. 1). These higher doses occasionally produced improvement in delayed response performance; however, improvement was only replicable in one animal (#124), who exhibited enhanced performance following both the 0.001 and 0.01 mg/kg doses. The 0.001 mg/kg dose also produced facial flushing in monkey #124, the only change in pallor noted in the study.

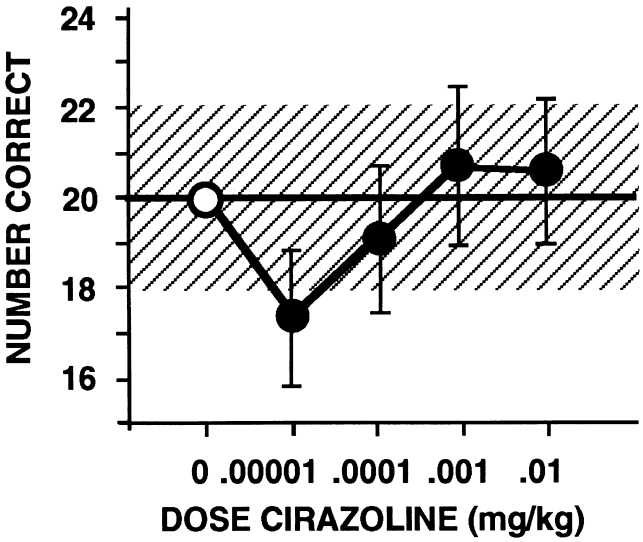

FIG. 1. Average response of the four aged monkeys to cirazoline treatment. Open circle represents the mean number correct from a possible 30 trials following vehicle+saline treatment; solid circles represent the mean + SEM number of trials correct following cirazoline (dose as indicated). Results are collapsed across all delay lengths. Stippled area represents the range of performance following vehicle+saline treatment.

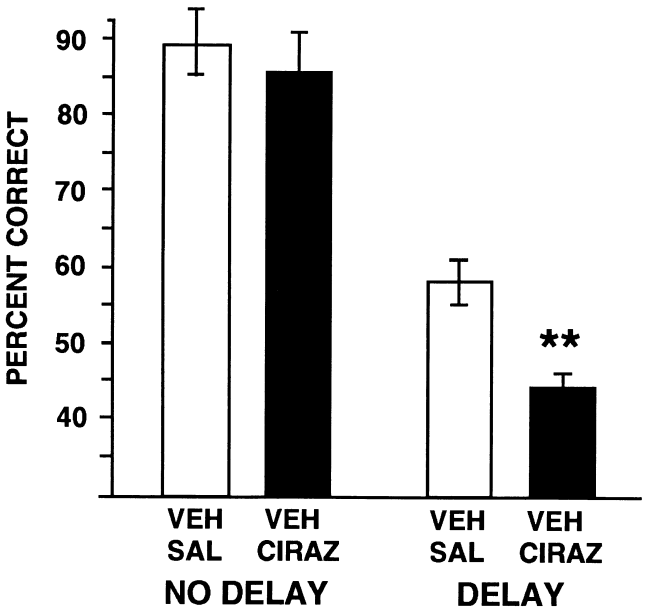

FIG. 2. Delay analysis of the impairment in delayed response performance induced by low doses (0.00001–0.001 mg/kg) of cirazoline. Cirazoline did not impair performance following "0" s delay trials (NO DELAY), but did impair performance following DELAY trials (given the small n, all delays greater than "0" s were collapsed together for the delay condition). Results represent mean + SEM percent correct for four aged monkeys. **significantly different from vehicle+saline treatment, $p = 0.017$; VEH = vehicle; SAL = saline; CIRAZ = cirazoline.

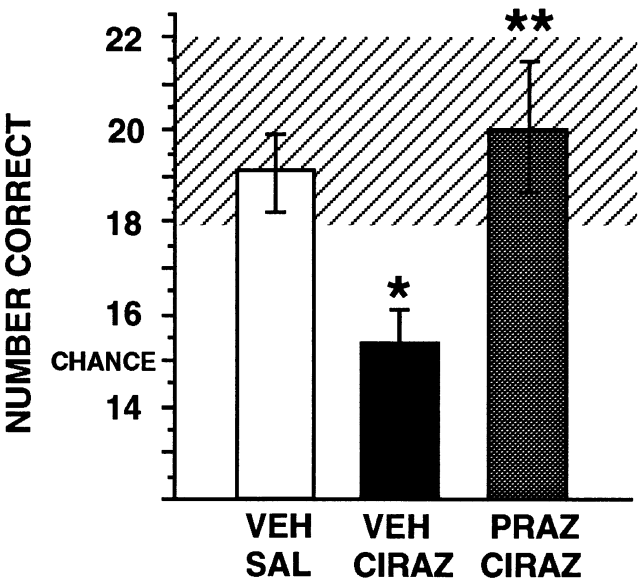

FIG. 3. Impairment in delayed response performance induced by a low dose (0.00001–0.001 mg/kg) of cirazoline was reversed by the alpha-1 adrenergic antagonist, prazosin. Results represent mean + SEM number correct from a possible 30 trials for four aged monkeys. Results are collapsed across all delay lengths. Stippled area represents the range of performance following vehicle+saline treatment. *significantly different from vehicle+saline treatment, $p = 0.017$; **significantly different from vehicle+cirazoline treatment, $p = 0.01$; VEH = vehicle; SAL = saline; CIRAZ = cirazoline; PRAZ = prazosin (0.1 mg/kg).

DISCUSSION

The results of this experiment indicate that low doses of cirazoline can impair delayed response performance in aged monkeys, whereas at higher doses impairment abates and is sometimes replaced by improved performance. The impairment in delayed response performance induced by low cirazoline doses likely involves an alpha-1 adrenergic mechanism, because it is readily reversed by the alpha-1 adrenergic antagonist, prazosin.

The improved performance following higher cirazoline doses was only observed reliably in one animal, and thus could not be examined properly for possible alpha-1 receptor mechanisms. However, it is of interest that the improvement in delayed response performance produced by 0.01 mg/kg cirazoline in this monkey was not reversed by pretreatment with prazosin, but was reversed by pretreatment with the imidazoline/alpha-2 antagonist, idazoxan (0.1 mg/kg; IM; 30 min). These preliminary findings suggest that the improvement in performance did not result from alpha-1 receptor mechanisms, but rather from nonalpha-1 receptor mechanisms (e.g., imidazoline or alpha-2 receptor actions). Further research with a larger number of animals and more selective imidazoline or alpha-2 receptor antagonists would be needed to clarify this issue.

The impairment in delayed response performance following low-dose cirazoline treatment appeared to result from changes in cognitive function rather than nonspecific changes in performance variables. This interpretation is based on the findings that cirazoline had no significant effect on performance on trials with "0" s delays, and had no significant effects on behavioral ratings of agitation, sedation, or aggression. Impairment also did not relate to changes in eating of the highly palatable food rewards, suggesting that altered motivation did not account for the impairment in performance following low cirazoline doses. Changes in eating in the home cage were not studied; thus, it is not known whether these relatively low doses of cirazoline (0.00001–0.01 mg/kg) altered ingestive behavior in the monkeys as higher cirazoline doses (0.05–0.4 mg/kg) do in rats (16). Further research with additional tasks would be needed to clarify the specificity of cirazoline's effects on cognitive functioning. Alpha-2 adrenergic agonists have been shown to improve performance of tasks dependent upon the PFC, but not the inferior or medial temporal cortex [reviewed in (10)]. It would be of interest to determine whether alpha-1 adrenergic agonists impaired PFC, but not posterior cortical, functions.

There are several speculations as to how alpha-1 receptor stimulation might result in spatial working memory deficits. NE has been shown to excite the ventral tegmental area (VTA) DA neurons through an alpha-1 receptor mechanism (19), and supranormal DA receptor stimulation in the PFC has been shown to induce spatial working memory deficits in rats and monkeys (3,7,24–26). This hypothesis could be tested by examining whether the cirazoline response could be reversed by low-dose DA antagonist pretreatment, or by agents such as (+)-HA-966, which decrease VTA cell burst firing and prevent the rise in PFC DA turnover (24–26). It is also possible that cirazoline's effects are mediated directly through drug actions in the PFC. Alpha-1 adrenoceptors, like alpha-2 adrenoceptors, are little effected by advanced age in the monkey PFC (11), and thus remain as a substrate for drug actions. Preliminary results indicate that infusion of the alpha-1 adrenergic agonist, phenylephrine, into the dorsolateral PFC of a young adult rhesus monkey impairs delayed response performance in a delay-dependent manner (29), similar to the results observed in the current study with systemic administration. In contrast, stimulation of alpha-2 receptors in the PFC improves working memory performance [(29), also reviewed in (10)]. These beneficial actions of alpha-2 agonists appear to result from drug actions at receptors postsynaptic to NE terminals, given that alpha-2 agonists become more rather than less effective in monkeys in whom the presynaptic element is destroyed with 6-OHDA (6) or reserpine (15). These data suggest that postsynaptic alpha-1 and alpha-2 receptors may have opposing roles in the PFC, as they do in the thalamus regulating arousal (14) and in the hypothalamus regulating ingestive behavior (16,22). Preliminary data comparing the binding of [^{3}H]-NE to recombinant human alpha-adrenoceptors suggests that NE has higher affinity for the alpha-2A subtype than for either the alpha-1A or alpha-1D subtypes (J. P. Hieble, personal communication). Thus, alpha-2 mechanisms may predominate when basal NE release is moderate (e.g., normal, attentive waking) and PFC function is optimal, whereas alpha-1 mechanisms may predominate under conditions of higher levels of NE release (e.g., during stress), contributing to PFC cognitive impairment. The results from the current experiment encourage continued research on NE alpha-1 mechanisms influencing higher cognitive function.

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