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Research report

Clonidine improves attentional and memory components of delayed response performance in a model of early Parkinsonism

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ABSTRACT

Cognitive deficits, including attention and working memory deficits, are often described in Parkinson's disease (PD) patients even during the early stages of the disease. However, cognitive deficits associated with PD have proven difficult to treat and often do not respond well to the dopaminergic therapies used to treat the motor symptoms of the disease. Chronic administration of low doses of the neurotoxin 1-methy,4-phenyl,1,2,3,6-tetrahydropyridine (MPTP) can induce cognitive dysfunction in non-human primates, including impaired performance on a variable delayed response (VDR) task with attentional and memory components. Since alpha-2 adrenergic receptor agonists have been suggested to improve attention and working memory in a variety of conditions, the present study assessed the extent to which the alpha-2 noradrenergic agonist clonidine might influence VDR performance in early Parkinsonian non-human primates. Clonidine (0.02–0.10 mg/kg) improved performance on both attentional and memory components of the task, performed in a modified Wisconsin General Test Apparatus, in a dose-dependent manner and the cognition enhancing effects of clonidine were blocked by co-administration of the alpha-2 noradrenergic antagonist idazoxan (0.10 mg/kg). These data suggest that clonidine or drugs of this class, perhaps with greater receptor subtype selectivity and low sedation liability, might be effective therapeutics for cognitive dysfunction associated with PD.

1. Introduction

Chronic administration of the dopaminergic neurotoxin 1-methy,4-phenyl,1,2,3,6-tetrahydropyridine (MPTP) in low doses can induce cognitive dysfunction without appearance of gross Parkinsonian motor deficits and may serve as a model of attentional and executive functioning deficits characteristic of a variety of disorders including Parkinson's disease [13,26], attention deficit disorder [30,33] and chronic schizophrenia [28,29]. Among the functional deficits induced by chronic low dose MPTP (CLD MPTP) administration is impaired performance on delayed response tasks [32,35]. Delayed response tasks have been classically used to assess spatial working memory in non-human primates under a variety of conditions. Working memory is an essential aspect of higher cognitive processes [6,22,38] and generally refers to the executive and attentional aspect of short-term memory (i.e., the ability to remember information over a brief period of time) and involves the ability to hold and manipulate information on line and then retrieve- the information. Working memory tasks typically include the active monitoring or manipulation of information or behaviors. Spatial working memory (SWM), in the context of the performance of the delayed response (DR) task refers to the cognitive process by which the location of a previously seen stimulus is remembered during various delay periods before a response is required.

According to Baddeley and Hitch's [8] classic model of working memory, there are two "slave systems" (the phonological loop and the visuo-spatial sketch pad) responsible for short-term maintenance of information and a "central executive" that is important for directing attention to relevant information, suppressing irrelevant information and inappropriate actions, and for coordinating cognitive processes when multiple tasks must be performed simultaneously [7]. There is a close link between attention and working memory [18]. The goal directing of attention (in the context of the DR task, directing attention to the locations of spatial cues and ignoring any other internal or external sensory stimuli) is driven by the prefrontal cortex [16] and is closely linked to working memory capacity [18]. Interestingly, chronic low dose MPTP-treated monkeys display deficits in performing delayed response and variable delayed response tasks, but their performance can be significantly improved by lowering the attentional demands of the task. For example, the presentation of an attentional cue prior to presentation of the stimulus significantly improved performance suggesting that the deficit in performing this task was primarily related to an attentional deficit rather than a memory deficit per se [15].

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In another study that assessed attentional and central executive functioning in chronic low dose MPTP-treated monkeys, animals developed deficits in the ability to maintain a response set as well as shift attentional sets in a central executive task with principles similar to the Wisconsin Card Sorting Test [13]. Animals also displayed deficits in performing other tasks and their behavior was marked by inattentiveness, difficulty in sustaining attention, difficulty focusing attention, motor readiness and planning deficits, impaired time estimation and increased impulsivity.

Alpha-2 adrenergic receptor agonists have been considered as potential therapeutics for a variety of cognitive disorders including age-related cognitive decline, memory disorders (including Alzheimer's disease and Korsakoff's psychosis) and attention deficit disorder [5]. However, there have been few studies that have examined the potential of alpha-2 adrenergic receptor agonists to improve cognition in Parkinson's disease (PD) patients. Considering the attention-based cognitive deficit in early PD patients as well as in CLD MPTP-treated monkeys, the present study was conducted to assess the extent to which the alpha-2 noradrenergic agonist clonidine might influence performance of a SWM task (i.e., variable delayed response) that is capable of assessing attentional and memory components of performance.

2. Materials and methods

2.1. Subjects

Three adult *Macaca fasicularis*, approximate ages 7–10 years (weight 5.9–6.4 kg) previously administered low doses of MPTP-HCl (dose range: 0.05–0.1 mg/kg, i.v. over 99–178 days; cumulative MPTP doses = 14.4–36.1 mg) were used in this study. All animals had prior behavioral testing experience and had stable cognitive deficits at the time of this study. Behavioral testing occurred approximately 2.5 years after the last MPTP exposure. The procedures employed in this study were approved by the Institutional Animal Care and Use Committee at Thomas Jefferson University and the study was performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

2.2. Cognitive testing

Behavioral testing took place in a modified Wisconsin General Test Apparatus (WGTA). Animals sat in a sound-attenuating chamber behind an opaque screen that, when raised, permitted access to a sliding tray. Background white-noise was provided. For the variable delayed response (VDR) task, a tray containing two recessed food wells with sliding red Plexiglas covers was used. Animals were trained to slide the cover and retrieve food from one of the wells after observing the experimenter bait the well. Right and left wells were baited in a balanced, quasi-random order. Five different delay lengths were used (ranging from 2 s to 30 s to yield approximately chance performance at the longest delay) to make up a daily testing session which consisted of 50 trials, ten at each of five different delay intervals. Baseline criterion for the CLD MPTP-treated monkeys was stable performance for five consecutive days with 10% or less variability.

2.3. Drug administration

Clonidine was diluted in sterile saline immediately before each drug trial and injected intramuscularly 40 min prior to testing. The doses used (0.02 mg/kg, 0.05 mg/kg, and 0.1 mg/kg) were selected based on previously published work reporting efficacy of clonidine in adult monkeys (aged 4–15 years) performing a delayed response task [17]. To assess the specificity of any response to clonidine, the alpha-2 noradrenergic antagonist idazoxan was administered in conjunction with clonidine on some trials. In these instances, idazoxan (0.1 mg/kg; i.m.) was administered immediately prior to administration of a dose of clonidine that provided significant improvement in task performance. This dose of idazoxan had been previously shown to attenuate beneficial effects of clonidine in monkeys performing tests similar to that used in the current study [4,17]. Drug trials were repeated twice and control or vehicle sessions were performed prior to and following drug tests. Administrations of clonidine occurred at least five days apart. In addition, due to the potential sedative effects of clonidine, animals were also rated for sedation during testing, using a previously described scale, where 0 = normal; no sedation, 1 = quieter than normal, 2 = sedated; drooping eyelids, slowed movements, 3 = intermittent sleeping, and 4 = too sedated to test [5,17].

2.4. Statistical analysis

Task performance following clonidine administration was compared with matched control performance data. Animals served as their own controls and statistical analyses used a repeated measures one-way analysis of variance (ANOVA) and pair-wise post hoc comparisons (Neuman–Keuls test) of vehicle/control and drug performance. Sedation data were analyzed using a non-parametric Wilcoxon test.

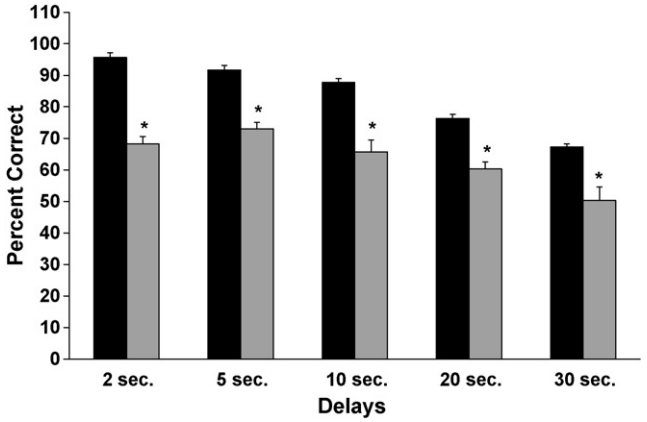

Fig. 1. Variable delayed response (VDR) performance in monkeys before (black bars) and after (gray bars) chronic low-dose MPTP administration. Prior to MPTP exposure, there was a delay-dependent decrease in task performance. After MPTP exposure, there was a general decrease in performance accuracy on both short and long duration delay trials. $^{*}p < 0.05$ compared to corresponding pre-MPTP performance. Bars show means ± S.E.

3. Results

Prior to MPTP exposure, all animals showed a delay-dependent decrement in performance on the VDR task (Fig. 1). Following MPTP exposure, overall performance significantly worsened [$F(2, 29) = 9.8408$, $p < 0.0001$] and showed a delay-independent pattern of performance. That is, animals performed significantly worse at all delays, compared to pre-MPTP baseline, and performed almost as poorly on short delay trials as on long delay trials (Fig. 1).

Clonidine administration improved overall task performance (all delays averaged together) [$F(3, 16) = 11.64$, $p = 0.0003$] in a dose-dependent manner (Fig. 2). The intermediate dose of clonidine (i.e.,

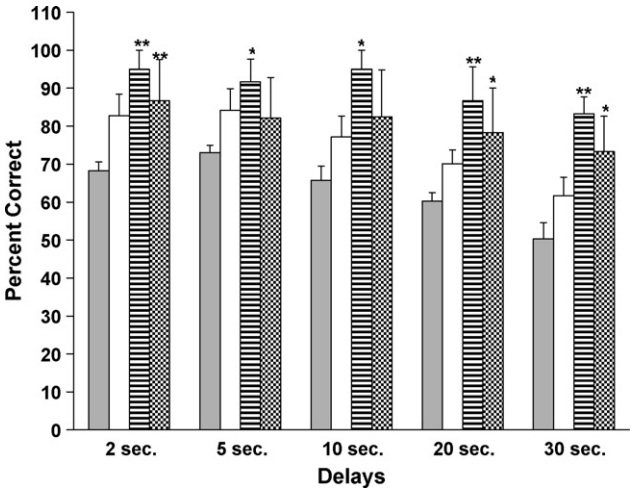

Fig. 2. Effects of clonidine on VDR performance. The lowest dose of clonidine used (0.02 mg/kg) slightly enhanced performance (unfilled bars), compared to MPTP baseline performance (gray bars) but did not result in a statistically significant improvement in performance at any delay. The intermediate dose of clonidine (0.05 mg/kg) significantly improved task performance at all delays (bars with horizontal lines), compared to MPTP baseline performance. Performance after administration of the highest dose of clonidine (0.10 mg/kg) was variable and was statistically significantly different from baseline only at 2, 20 and 30 s delay trials (checkered bars). $^{*}p < 0.05$ versus corresponding MPTP baseline; $^{**}p < 0.01$ versus corresponding MPTP baseline. Bars show means ± S.E.